MEDICAL LIBRARY

THE JOURNAL OF CLINICAL ENDOCRINOLOGY

JAN 25 1950

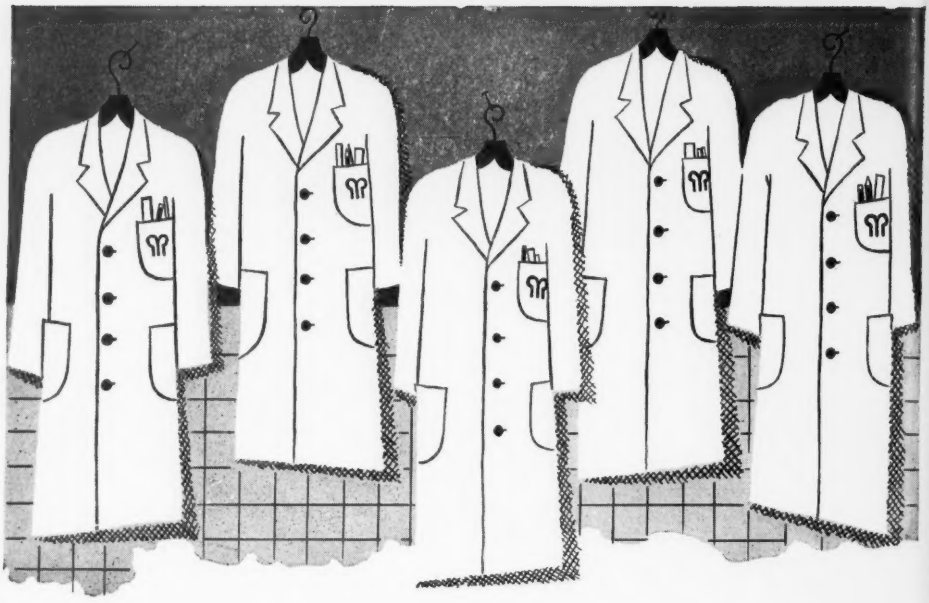
VOLUME 9 NUMBER 12

Next Annual Meeting, San Francisco, California, June 23 and 24, 1950

DECEMBER 1949

DEVELOPMENT OF SPERMATOGENESIS IN HYPOGONADISM 1245
Lewis M. Hurxthal, Hans J. Bruns and Natalija Musulin
ELECTROLYTE BALANCE IN DIABETIC KETOSIS AND ACIDOSIS . . . 1259
Jonas Weissberg, T. H. McGavack, A. M. Shearman and I. J. Drekter
THE PROGESTERONE THERAPY OF HUMAN UTERINE LEIOMYOMAS . . 1273
Albert Segaloff, John C. Weed, William H. Sternberg and William Parson
SERUM PRECIPITABLE IODINE IN PITUITARY DISEASE 1292
J. P. Peters, W. J. German and E. B. Man
TESTOSTERONE; EFFECT ON BONY METASTASES FROM BREAST CANCER 1314
Frederick W. Preston, Samuel G. Taylor, III and Joseph L. Crumrine
INTRAORAL DCA TABLETS IN TREATMENT OF ADDISON'S DISEASE . . 1324
Evelyn Anderson, Laurance W. Kinsell, Troy C. Daniels and Edward Henderson
RUDIMENTARY TESTES, DWARFISM & CONGENITAL MALFORMATIONS . 1333
J. Reforzo-Membrives, A. Trabucco and F. Escardó
PRECOCIOUS PUBERTY ASSOCIATED WITH OVARIAN DYSGERMINOMA 1349
A. M. Hain
VAGINAL SMEAR GLYCOGEN: LIMITATIONS AS INDEX OF ESTROGEN . 1359
W. Burton Ayre and J. Ernest Ayre
SMEARS FROM FEMALE URETHRA AND SMEARS OF URINARY SEDIMENT 1362
E. B. del Castillo, Joaquin Argonz and Carlos Galli Mainini
CARE AND MAINTENANCE OF TOADS AND FROGS FOR PREGNANCY TEST 1372
Maria Isabel Mello
DISTRIBUTION OF RADIOIODINE IN PATIENT WITH THYROID CANCER . 1379
Joseph E. Rall, F. Raymond Keating, Jr., Marschelle H. Power and Warren A. Bennett
LABELED THYROGLOBULIN AND THYROXINE IN MYXEDEMA 1392
A. Albert, Joseph E. Rall, F. Raymond Keating, Jr., Marschelle H. Power and Marvin M. D. Williams
RADIOACTIVE *d-l*-THYROXINE ORALLY AND INTRAVENOUSLY 1406
A. Albert and F. Raymond Keating, Jr.
SURGICAL TREATMENT OF CARCINOMA OF THE THYROID GLAND . . 1422
B. Marden Black
EDITORIAL: The Thyroid-Pituitary Apparatus as a Servo (Feed-Back) Mechanism . 1429
R. G. Hoskins
LETTERS TO THE EDITOR:
Thyrotoxicosis Factitia 1432
J. H. Means
Testosterone and Development of Axillary Hair 1434
A. S. Albrieux and J. C. Mussio Fournier
Urinary Corticosteroid Excretion in Pre-Eclampsia and Eclampsia 1436
Raymond Devis and Marthe Devis-Vanden Eeckhoudt
THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS
POSTGRADUATE ASSEMBLY IN ENDOCRINOLOGY 1438
THE 1950 ANNUAL MEETING 1439
THE 1950 AWARDS AND FELLOWSHIPS 1440
THE AMERICAN GOITER ASSOCIATION
THE 1950 ANNUAL MEETING 1442
THE 1950 VAN METER PRIZE AWARD 1442
AUTHOR INDEX TO VOLUME 9 1443
SUBJECT INDEX TO VOLUME 9 1455

Issued monthly for The Association for the Study of Internal Secretions by Charles C Thomas, Publisher. Annual subscription, $11.00; single copies, $1.00



The mantles of the men who want a better thyroid

They seek better thyroid therapy and so they offer PROLOID

1. Extracted from fresh thyroid material and carefully assayed for potency so that the different thyroid batches can be balanced and then blended for more uniform ultimate potencies.

2. So purified of unwanted organic matter as to be free from the tell-tale odor of ordinary thyroid.

3. Standardized *metabolically* as well as chemically to guard the patient against metabolic fluctuations.

Available in ¼, ½, 1, 1½ and 5 grain tablets—bottles of 100, 500 and 5,000. Also as powder—1 oz. and 8 oz.

Proloid THE IMPROVED THYROID MEDICATION

CHILCOTT
Laboratories DIVISION OF The Maltine Company
MORRIS PLAINS, NEW JERSEY

The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 9 DECEMBER, 1949 NUMBER 12
Copyright 1950 by the Association for the Study of Internal Secretions

DEVELOPMENT OF SPERMATOGENESIS IN HYPOGONADISM

LEWIS M. HURXTHAL, M.D., HANS J. BRUNS, M.D.* AND NATALIJA MUSULIN, M.D.

From the Department of Internal Medicine, The Lahey Clinic, Boston, Massachusetts

THE development of spermatogenesis with mature spermatozoa in eunuchoidism or hypopituitarism is generally considered unlikely, if not impossible. In many cases of eunuchoidism as well as in panhypopituitarism the testes show degenerative changes and appear incapable of regeneration. Occasionally this condition may be suspected by their small size and frequent very soft consistency. Biopsy of the testis in such cases should indicate those testes which are capable of stimulation but the final test of sperm maturation is made by actual treatment.

One of us (1) reported briefly on the development of spermatogenesis in a male considered to have arrest of testicular development at pubescence. This case is presented here with further observations. Heller and Nelson (2) have recently reviewed this subject; they have also obtained spermatogenesis in eunuchoid individuals. They point out a fact which we too have observed and one which confirms a principle in endocrine therapy which has long been doubted, namely the existence of "priming." In other words, in some cases continued substitution therapy is not necessary, and secondary sex characteristics, including spermatogenesis, have not shown evidence of regression after cessation of treatment.

It is now common knowledge that chorionic gonadotropin will stimulate responsive gonads in males and initiate pubescence or speed the process

Received for publication May 12, 1949.

* Fellow in Internal Medicine. Now practicing in Syracuse, New York.

along, when given during the ages of 9 to 16; and that on stopping treatment there is continued development to maturity. Testosterone has been found to do the same (3). The criticism of this treatment has always been that sexual development would have eventually occurred without therapy. This objection is perfectly valid, as has been frequently proved. Obviously, however, it is impossible to make control observations of these cases and although it may be stated that sexual maturity will develop without

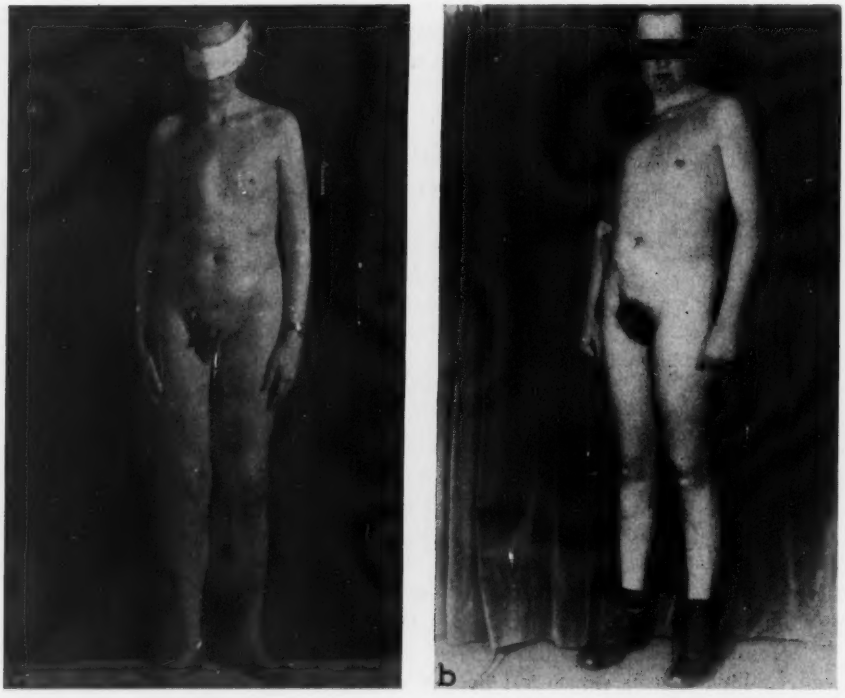


FIG. 1. *Case 1. a.* Eunuchoidism in a male aged 21. Photograph taken in 1936, before therapy with testosterone. *b.* Appearance in 1939. He is now the father of 2 children.

therapy, in most instances of delayed puberty it is unlikely that sexual maturity would have developed as quickly. It has not been our custom in the past to advise treatment in cases of delayed puberty, but we have frequently seen youths who have been treated elsewhere with chorionic gonadotropin, whose history indicated a prompt stimulation of genital development, followed by progression to maturity when therapy was stopped.

Such observations, including those of the cases to be reported here as

well as other phenomena noted in endocrine problems, have led us to conclude that the priming principle is an actuality.

The purpose of this communication is to report 4 patients in whom spermatogenesis appeared to have been the result of treatment and 1 case in which it seemed likely that fertility might have been present but after disappearing, was not restored a second time during the period of observation.

CASE REPORTS

Case 1.—This patient, in whom spermatogenesis occurred with the administration of testosterone propionate, was a eunuchoid man of 21 years who had small but rather firm testes, without the development of secondary sexual characteristics (Fig. 1). He was treated initially with testosterone propionate by injection and later with oral methyltestosterone. Satisfactory development of all secondary sexual characteristics followed. Several years later the patient married, had satisfactory sexual intercourse, and ten months after his marriage his wife gave birth to a healthy normal boy. Testicular biopsies were not made on this patient nor could samples of semen be obtained because of his religious beliefs. In view of the enlargement of the testis after the use of testosterone and the excellent general response to this preparation, we felt, but of course could not prove, that spermatogenesis had occurred. The details of this case are as follows:

The patient, 21 years of age, was admitted to the Lahey Clinic on May 1, 1936. The family history was not pertinent. Past medical history revealed that he had had a ruptured appendix at the age of 21, scarlet fever at 13 and mumps at 15 without known orchitis. His chief complaint was failure of sexual development. He also had noted an occasional hot flash. His height was 72⅛ inches (without shoes) and span 74½ inches; the pubis to floor measurement was 37½ inches. His weight was 197 pounds (Fig. 1*a*).

Urinary follicle-stimulating hormone tests gave negative results. At that time (1936) no effect could be obtained on spermatogenesis in immature male mice or on the vaginal smear of immature female mice. 17-Ketosteroid determinations were not being done in 1936.

Roentgenograms showed a bone age of approximately 16 or 17 years of age (Todd's standards).

Treatment consisted of injections of testosterone propionate, 25 mg. every five days; later the dose was increased to 25 mg. every three days. This treatment was begun in October 1938, and his condition as of December 1939 is shown in Figure 1*b*. In 1940 his height was 74¼ inches and span 75½ inches. At this time he discontinued testosterone propionate and took 10 mg. of methyltestosterone by mouth daily until 1944, when he was married; at that time he weighed 220 pounds and there was no further longitudinal growth. He developed a light beard and a small mustache and shaved twice a week. His voice was deep and he developed great confidence in himself and no longer had periods of depression. His testes were relatively normal in size. In January 1945, his wife delivered a normal boy. The patient continued to take 10 mg. of methyltestosterone irregularly without noticeable regression of sexual function. In 1948, a second child was born.

Case 2.—An unmarried discharged veteran, 25 years of age, first consulted Dr. George Quigley[1] of Newton, Massachusetts, who reported that the patient was definitely

[1] The authors are indebted to Dr. Quigley for permission to study this case and report it here.

eunuchoid with an unchanged voice and very scant pubic and axillary hair. The penis and testes were small. The patient had no interest in sexual matters. He was treated by Dr. Quigley with intramuscular testosterone propionate for a period of two months, then with methyltestosterone 20 mg. orally for ten and a half months. During this time he developed rapidly, the penis and testes enlarged in size, the pubic and axillary hair increased and facial lanugo appeared (Fig. 2). At the end of the twelve and a half months of treatment, an ejaculated specimen showed numerous active spermatozoa. Previous to therapy he was unable to ejaculate. Sexual function became normal. Medication was then discontinued and ten months later an ejaculated specimen showed 90 million spermatozoa per cubic centimeter. At the present writing there has been no regression in secondary sex characteristics. The last sperm specimen (December 8, 1948) showed 120 million per cubic centimeter. Details of this case are as follows:

FIG. 2. *Case 2.* A eunuchoid male, aged 25, after one year of testosterone therapy. He showed development of spermatogenesis with treatment, and maintenance of spermatogenesis without further therapy. Before therapy, when his age was 24, his skeletal age was 16.3 years.

No genital development was noted from the age of 10. Growth remained stationary throughout high school, then the patient began to grow (age 18). He was rejected for military service at the age of 21 because of an endocrine disturbance. Later he was accepted and spent three years in the Air Corps. His voice remained high-pitched, no shaving was necessary and there was very little pubic and axillary hair. The genitalia were small. He had no libido, few erections and no ejaculations.

When the patient was first seen by Dr. Quigley and before treatment, a roentgenogram of the wrist was taken which showed ununited epiphyses (Fig. 3*a*). The bone age was 14 years 9 months.

When first examined in the Lahey Clinic June 13, 1947, through the courtesy of Dr. Quigley, the patient's height was 74⅝ inches, span 80 inches, and weight 161 pounds. The hemoglobin was 85 per cent, and erythrocyte count 5,400,000; the urine (unconcentrated) showed no FSH, but 17-ketosteroids were 10.1 mg. per twenty-four hours (one month after cessation of treatment). Urinary 17-ketosteroids eleven months after cessation of treatment were 13.6 mg. per twenty-four hours. The bone age was 16 years 3 months. Twenty-three months after cessation of treatment the patient weighed 167 pounds, the height was 75⅞ inches, and span 81½ inches. The voice was deep, he shaved once a week, and hair growth was beginning below the umbilicus. Sexual drive was normal.

Observations in December 1948 were as follows: Sperm count was 120 million per cubic centimeter, total 360 million, 80 per cent motile; 50 per cent motility twenty-four hours later; 20 per cent of motile sperms were abnormal and 60 per cent of nonmotile sperms were abnormal. The bone age was 18 years 6 months (Fig. 3*b*). The urine gave a weakly positive reaction for FSH but this increased to a positive reaction when the

FIG. 3. *Case 2. a.* Roentgenograms of hand and wrist showing open epiphyses before treatment (left). *b.* Their closure after two years of therapy.

urine was concentrated twice. Urinary 17-ketosteroids per twenty-four hours were 17.6 mg.

Case 3.—This patient was a boy of 18 who was rejected temporarily by the Armed Forces in 1945 because of retarded sexual development. On examination, his sexual development was that of an average 15-year-old boy (Fig. 4*a*). Late appearance of puberty was considered a possibility and on our recommendation he was reconsidered and accepted in the Air Corps where he served two years in a ground crew. When discharged from the Service he consulted us again and there was little or no progress in his genital development as judged from a photograph taken on the first examination. He had not shaved; his voice had not changed. Ejaculation was possible but there was very little semen and it contained no spermatozoa. A testicular biopsy was done (Fig. 5). He was then given chorionic gonadotropin, 1,000 units daily for a period of one month. During the treatment there was a noticeable increase in penile erections and ejaculate, but no spermatozoa were found. Methyltestosterone, 30 mg. a day, was prescribed for one month, at which time 2 or 3 sperms were found per high power field. One month later the sperm count was 1,500 per cubic centimeter. Following this he was given testosterone, 300 mg., by pellet implantation. He continued to develop, with a deepening of voice

and growth of hair on the face; the penis became larger and his body contour changed. Pellets were renewed subsequently and no further treatment was given after June 1947. The sperm count on this date was 55 million per cubic centimeter. Six months later, without further therapy, the sperm count was 88 million per cubic centimeter with 45 per cent motility. Nonmotile sperms showed large round heads. In June 1948, a sperm count was 216 million per cubic centimeter with 35 per cent motility (Fig. 4*b*).

At this time the patient's voice had become deep in quality, he shaved once a week, and had normal sex interest. He resumed methyltestosterone orally for one month and

FIG. 4. *Case 3. a.* Midpuberal arrest of sexual development in a male, aged 20, showing condition before therapy. *b.* After two years of therapy. Normal sperm counts were maintained without treatment.

he had several nocturnal emissions, a phenomenon which had not been noted previously. These emissions did not occur again when medication was discontinued. Additional data are as follows:

Past history: The patient had mumps when about 8 years of age. He had a ruptured appendix at 9, requiring two operations for drainage. Obesity of the abdomen and legs was noted at 12 years. He had no beard; pubic and axillary hair first appeared at about 13 years of age but there was practically no increase thereafter. He had occasional erections.

On November 28, 1944, his height was 5 feet 8 inches, span 5 feet 8 inches, and weight 153 pounds. Urinary 17-ketosteroids were 7 and 7.8 mg. per twenty-four hours. There was no urinary FSH in an unconcentrated specimen. His bone age was 15.3 years. The

sella was of normal size. Testis volume was 13 cc. Routine urine and blood tests gave normal results.

January 1947 (before treatment), the height was 5 feet 9 inches, span 5 feet 11¼ inches, and weight 167 pounds. Bone age was 16.3 years (1 year increase in three years). Testis volume was 13 to 18 cc. The test for urinary FSH was unsatisfactory. Urinary 17-ketosteroids were 10.4 mg. per twenty-four hours.

August 5, 1948, the height was 71 inches, span 70 inches, and weight 167 pounds. Bone age was 17.3 years.

FIG. 5. *Case 3.* Biopsy specimen of testis before therapy. Leydig cells are few. Note slight peritubular thickening and "immature" tubular elements.

Case 4.—A man, aged 43, with idiopathic panhypopituitarism, complained of gland trouble and failure to ejaculate and stated that he had never really needed to shave and that his public hair had fallen out; otherwise he was normal. He had received treatment with chorionic gonadotropin and later small amounts of testosterone propionate for six months by Dr. J. A. K. Cunningham of Christchurch, New Zealand. The details of this case and a photograph of the patient were published in the *New Zealand Medical Journal* (4). After about one month of treatment he was able to produce a small ejaculate.

From his history, it was apparent that he had progressed normally until about the age of 16 when he developed severe asthma which lasted one year. He stated that he stopped growing at that time. He had sufficient sex interest to get married at the age of 35; intercourse was fairly satisfactory from the beginning, occurring about once a week but never with ejaculation. At the age of 43, this man appeared as a youth of 18 to 20 years. His physical status before therapy is shown in Figure 6*a*. The radial epiphyses were

were still open and testes and penis were within normal limits of size (he had received only limited testosterone therapy in New Zealand). All evidence pointed to the presence of a panhypopituitarism. Treatment consisted of chorionic gonadotropin and methyltestosterone for approximately two years, during which time in several ejaculated specimens no spermatozoa were found. He was rejoined in this country by his wife from whom he had been separated for two years because of the War. Sexual relations were greatly improved and three months later he reported that his wife was two months pregnant.

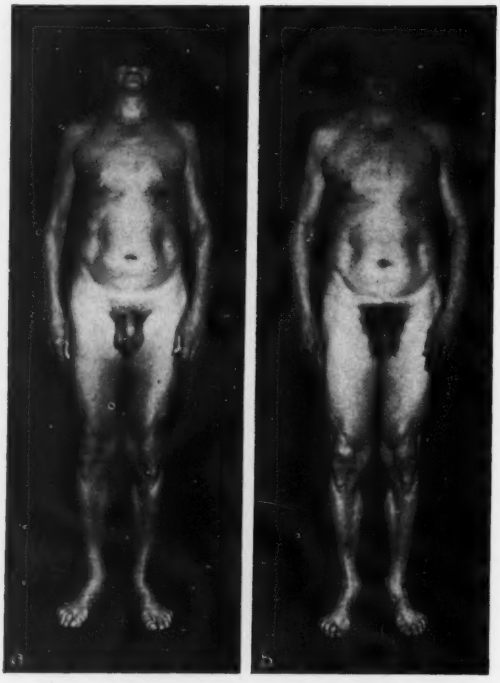


FIG. 6. *Case 4.* Age 43. Panhypopituitarism, of unknown etiology, beginning at age 16. *a.* Condition before therapy in this country, after a limited course of testosterone abroad. *b.* Two years later, after therapy with chorionic gonadotropin and testosterone. Spermatogenesis occurred and he is now the father of one child.

An ejaculated specimen at this time showed 50,000 active spermatozoa per cubic centimeter. This patient later showed a larger number of spermatozoa and continued to take methyltestosterone, 10 mg. a day. The following are some of the data obtained in this case at various intervals:

The patient's height was 65 inches, span 67 inches, weight 143 pounds, blood pressure 120 mm. systolic and 80 mm. diastolic, pulse 56, basal metabolic rate −22 per cent, and plasma cholesterol 264 mg. per 100 cc. The hemoglobin was 12.4 Gm., red count 4,100,000, and white count 4,100; the differential showed polymorphonuclears 47.5, lymphocytes 40, monocytes 6 and eosinophils 7.5. Urinary FSH tests gave negative results in unconcentrated specimens. On one occasion a positive FSH was obtained while

the patient was taking injections of chorionic gonadotropin. The urinary 17-ketosteroid output was 3.6 mg. per twenty-four hours. The water test for adrenal deficiency was positive. The patient was able to ejaculate a small amount of semen which had no spermatozoa. Bone age was 16 years; the sella was normal in size.

Treatment consisted of chorionic gonadotropin, 6,000 or 7,000 units per week, and methyltestosterone, 20 mg. orally per day. This therapy was given from November 1944 until July 1945 when the chorionic gonadotropin was reduced to 4,000 units per week.

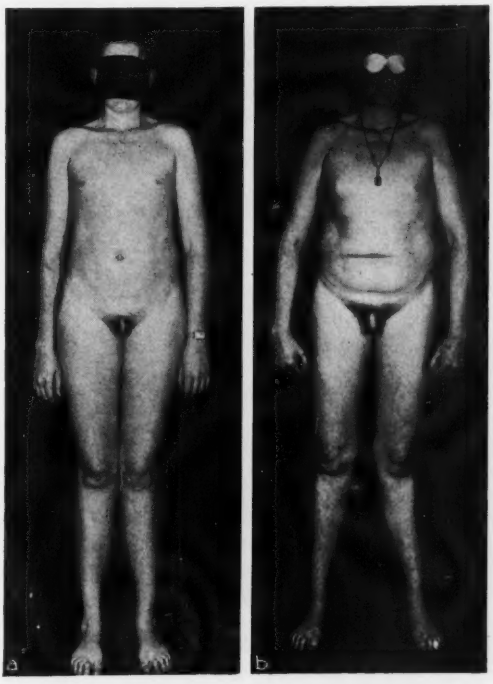


FIG. 7. *Case 5. a.* Eunuchoidism in a male aged 24, in 1936, before therapy. *b.* Condition after resumption of testosterone therapy in 1947 (*see* text).

During this time the patient noted increased erections, increased general strength, and beginning of the return of pubic and axillary hair. From December 1945 to June 1946 he continued taking chorionic gonadotropin, 4,000 units per week, and had reduced the methyltestosterone to 10 mg. per day. In addition, during this period he took ½ grain of thyroid a day. At this time another ejaculated specimen showed no spermatozoa. There was some hair in the axillary and pubic regions. The testes were larger.

From June 1946 to November 1946 the patient took methyltestosterone, 20 mg. a day. At this time, when his wife was pregnant, the ejaculated specimen showed 50,000 spermatozoa per cubic centimeter. In June 1947, his wife delivered a normal boy. He continued to take methyltestosterone but on two occasions had implantations of testosterone pellets, 150 mg. at a time, which the patient felt produced a better effect than

when given orally. He shaved more frequently and felt well in every way. The radial epiphyses were closed. The sperm count in June 1947 showed 850,000 per cubic centimeter (Fig. 6*b*).

On January 7, 1949, the patient's height was 66 inches and weight 165 pounds. He was taking 100 mg. a week of methyltestosterone but had taken no thyroid for five months. He shaved every other day. There had been some return of asthma and hay fever in August and September during the preceding two years, but otherwise he was in excellent health.

FIG. 8. *Case 5.* Biopsy specimen of testis before resumption of testosterone therapy in 1947, showing tubules somewhat widely spaced, no hyaline or peritubular sclerosis, and a few islands of Leydig cells. The tubules appear capable of stimulation, although no spermatozoa were demonstrable in the semen while the patient was under treatment. There may be a few spermatozoa in the tubules.

Case 5.—The fifth case, perhaps less convincing, is that of a male with typical eunuchoidism. He was first seen in 1936 (Fig. 7*a*). With small doses of testosterone, not over 5 mg. three or four times a week, he made some improvement and was married; he stated that marital relations were satisfactory. In 1940 he received about 50 mg. of testosterone propionate a week for five weeks. Treatment was then given up. From June 1943 until October 1946, he took 40 mg. of methyltestosterone daily. Twenty-one months after beginning this therapy his wife became pregnant and later gave birth to a normal child. He was forced to discontinue the use of testosterone in October 1946 because of expense, and reported here two months later. At that time his condition seemed improved (Fig. 7*b*) over that in 1936. Testicular biopsy was done and the specimen showed hypo-

plasia. There were a few Leydig cells (Fig. 8). No degenerative changes of any consequence were noted in the testes. Spermatids were present and possibly rare spermatozoa in the tubules.

After treatment with testosterone pellets, 225 to 300 mg. at each implantation from January to May 1947, there was a return of his sexual competency, increased ejaculate and regrowth of pubic hair, but several specimens of semen including one in May 1947 had no spermatozoa. When it was first learned that the patient's wife became pregnant after testosterone therapy, we had little doubt that the husband was the father, in view of our observations of the other cases herein described. The testicular biopsy, done when no testosterone had been used for six months, further convinced us that spermatogenesis was possible in this case. After another intensive course of treatment with testosterone by pellet implantation, however, there was very little increase in size of the testes and spermatozoa were never found in the ejaculated specimens. There may have been some blockage to the exit of spermatozoa, or else testosterone propionate was less effective than methyltestosterone. Another possibility to be considered is that perhaps the amount of testosterone administered by pellet implantation was too large. Subsequent observations could not be made because of distance; but, considering the length of time required in other cases, it is likely that spermatozoa might have been found at a later date. At the present writing the patient is under treatment with chorionic gonadotropin, without evidence of spermatogenesis.

Additional data in this case are as follows: When first seen in 1936, the patient complained of tiredness and belching. The genitalia were small. He had had an appendectomy at the age of 17, but no other illness. During the early part of 1936 he received two injections a week of pituitary hormone, following which he gained 20 pounds.

On examination in 1936 (Fig. 7*a*) his height was 72⅛ inches, span 74⅝ inches and weight 172 pounds. The bone age was 16 years; all epiphyses of the hand and wrist were open. Tests for urinary FSH and estrin gave negative results. The sella was normal. The hemoglobin was 86 per cent and erythrocyte count 4,100,000. In 1947 (Fig. 7*b*) the height was 73 inches, the span 77 inches and he weighed 192 pounds. The epiphyses of the hand and wrist were closed; the iliac crests were not fused. There was no urinary FSH but 17-ketosteroids were 8 mg. per twenty-four hours. The hemoglobin was 94 per cent, red blood count 4,170,000 and plasma cholesterol 125 mg. per 100 cc.

DISCUSSION

Since excess of follicle-stimulating hormone (FSH) was not found in any of these patients, it is assumed that the primary disturbance in these cases was not in the testis—at least not in the tubular portions. Follicle-stimulating hormone is thought to be the trophic agent of the tubules, but LH (luteinizing or interstitial cell-stimulating hormone) through which testosterone or male sex hormone is produced is necessary for maturation of the spermatozoa. Heller and Nelson (2) have shown that cases of hypogonadotropic eunuchoidism, comparable to some of the cases described herein, will respond to preparations of purified FSH. Their patients were given chorionic gonadotropin which contains both FSH and LH, but this alone did not produce complete spermatogenesis. A special preparation of purified FSH was then given and examination of seminal fluid and testicular biopsy indicated that spermatogenesis had been stimulated. As

stated before, this same phenomenon was observed by us after preliminary use of chorionic gonadotropin followed by testosterone, and with testosterone alone. The question arises, therefore, whether additional FSH is really necessary to promote spermatogenesis in these cases or whether only a small amount of secreted FSH is required along with administered testosterone. A further possibility is that testosterone given in small or moderate doses may stimulate FSH or, if the latter is present, luteinizing hormone. In hypophysectomized adult male rats, testosterone alone is said to maintain spermatogenesis.

There is some difference of opinion as to whether or not testosterone inhibits follicle-stimulating hormone. In a patient with excessive FSH and eunuchoidism, due either to cryptorchid testes or anorchia, we found (5) that testosterone therapy over a period of several years decreased greatly the amount of FSH as well as the excessive 17-ketosteroids. Heller and Nelson (6) also demonstrated a reduction in FSH on giving testosterone propionate, but did not find this reduction in another case in which free testosterone was implanted as pellets.

In hypogonadotropic eunuchoidism, three or four hormonal variations must be considered. In all cases, there must be a deficiency in testosterone or male sex hormone; this deficiency might be due to an absence or deficient elaboration of luteinizing hormone secretion by the pituitary, producing a failure of male sex hormone. Another likelihood is failure of Leydig cells to secrete, or failure of their precursors to become Leydig cells, even when adequate luteinizing hormone is present. This possibility is to be considered because of the experimental data suggesting that, in some species and perhaps in humans, Leydig cells do not react to gonadotropins—at least until a certain stage of maturity has been reached. On the other hand, the fetal testes are thought to have an abundance of Leydig-like cells due to the excess quantities of circulating chorionic gonadotropin during pregnancy. A combined follicle-stimulating hormone and luteinizing hormone failure is another variation which is probably exemplified in Case 4.

The cases described by McCullagh (7), in which there was evidence of hypoleydigism but at the same time adequate FSH, provide evidence that variations in these two hormones need not coincide. Furthermore, we have observed menstrual bleeding in females, with or without pituitary tumor, produced by the sole use of progesterone. This bleeding may be due, in some instances at least, to luteinizing hormonal failure; vaginal smears in such cases show estrogenic effect. In the male, the tubules may be unable to use FSH unless there is adequate Leydig cell function.

The surprising phenomenon is that some of these eunuchoid patients continue to have normal glandular function after cessation of hormonal

therapy. It would appear that a priming effect can be obtained by giving either chorionic gonadotropin or testosterone alone. The explanation may ultimately be found in a hormone-enzyme relationship about which little or nothing is known so far as the testes are concerned.

One criticism which is to be anticipated concerning the cases reported here, as well as those reported by Heller and Nelson (2), is that sexual development might have taken place spontaneously. In every case there was prompt improvement coinciding with treatment. It seems to us that the above mentioned criticism is untenable for the entire group, especially in the case of the 43-year-old man (Case 4).

In eunuchoidism, therefore, in which condition the testes are small but of normal contour and firmness, a trial of chorionic gonadotropin is worthwhile; and if there is response, testosterone may be substituted in the hope of continued spermatogenesis. These patients should have a testicular biopsy to check on the likelihood of a favorable effect from treatment. Assays for urinary gonadotropin should reveal excess quantities when there is primary testicular disease. In such cases, therapy with chorionic gonadotropin would probably not be effective. A trial might be given, however, if the urinary gonadotropin is not in great excess, since the latter does not necessarily indicate the status of LH. Furthermore, testicular biopsy in some cases may not necessarily reveal the functional status of the testis.

CONCLUSION

Development of secondary sex characteristics and spermatogenesis may be brought about in some cases of hypogonadotropic eunuchoidism or panhypopituitarism in the male by treatment with testosterone alone. Chorionic gonadotropin, containing varying quantities of follicle-stimulating as well as luteinizing hormone, may bring about development of secondary sex characteristics and nitrogen retention through stimulation of the Leydig cells and, if continued long enough, may cause maturation of the spermatozoa (8, 9). Chorionic gonadotropin with, or followed by, testosterone apparently will do the same thing. Once these developments have occurred continued treatment apparently is not always necessary.

REFERENCES

1. Hurxthal, L. M.: Hypogenitalism during the usual time of puberty, *J.A.M.A.* **136:** 12–19 (Jan. 3) 1948.
2. Heller, C. G., and Nelson, W. O.: Classification of male hypogonadism and a discussion of the pathologic physiology, diagnosis and treatment, *J. Clin. Endocrinol.* **8:** 345–366 (May) 1948.
3. Dunn, C. W.: Diagnosis and treatment of testicular deficiency—male hormone therapy, *Med. Clin. North America* pp. 1867–1895 (Nov.) 1942.

4. CUNNINGHAM, J. A. K.: Testosterone therapy in eunuchoidism, *New Zealand M. J.* **45**: 35–43 (Feb.) 1946.
5. HURXTHAL, L. M., and MUSULIN, N.: Gynecomastia: a case associated with mixed tumor of renal origin and testicular atrophy, *Lahey Clinic Bull.* **4**: 38–44 (Oct.) 1944.
6. HELLER, C. G., and NELSON, W. O.: Hyalinization of seminiferous tubules and clumping of Leydig cells. Notes on treatment of the clinical syndrome with testosterone propionate, methyl testosterone and testosterone pellets, *J. Clin. Endocrinol.* **5**: 27–33 (Jan.) 1945.
7. MCCULLAGH, E. P., and KLINE, I. T.: Absence of pituitary failure in fat boys with testicular deficiency, *Cleveland Clinic Quart.* **13**: 10–17 (Jan.) 1946.
8. KENYON, A. T.; KNOWLTON, K.; LOTWIN, G.; MUNSON, P. L.; JOHNSTON, C. D., and KOCH, F. C.: Comparison of metabolic effects of testosterone propionate with those of chorionic gonadotropin, *J. Clin. Endocrinol.* **2**: 685–689 (Dec.) 1942.
9. LANDAU, R. L., and KNOWLTON, K.: The metabolic effects of chorionic gonadotrophins in young men, *J. Clin. Investigation* **27**: 545–546 (July) 1948.

ELECTROLYTE BALANCE IN UNCONTROLLED AND CONTROLLED DIABETIC KETOSIS AND ACIDOSIS*

JONAS WEISSBERG, M.D., T. H. McGAVACK, M.D., A. M. SHEARMAN, M.D.† AND I. J. DREKTER, B.S.

From the New York Medical College, Metropolitan Hospital Research Unit, New York

RECENT chemical studies, during the treatment of diabetic acidosis, have emphasized certain changes in electrolyte balance which warrant careful appraisal and possible therapeutic application.

Soon after the discovery of insulin, Harrop and Benedict (1), and shortly thereafter Briggs and co-workers (2), demonstrated a fall in the potassium level in the plasma when insulin was administered. In the early period after the introduction of insulin little attention was given to the fall of potassium following the administration of insulin, since the glycosuria, hyperglycemia and ketonuria were the factors deserving the greatest emphasis in the treatment of the diabetic state. In 1933 Atchley, Loeb and co-workers (3) noted electrolyte changes with a fall in plasma potassium in two diabetic patients upon withdrawal and then later re-establishment of insulin therapy. Shortly thereafter Elkinton and co-workers (4), and the Wileys (5) noted a fall in plasma potassium in states of diuresis and dehydration. This led to Darrow's (6) therapeutic regimen for replacing the large losses of potassium seen in the diarrheas of infancy. In 1937 when Bellet (7) noted the electrocardiographic changes during emergence from diabetic acidosis there was a revival of interest in electrolyte balance in diabetes. In 1946 Holler (8) reported a patient who was vigorously treated for diabetic acidosis, and developed a respiratory paralysis due to a critically low level of potassium in the plasma, with recovery after the administration of a solution of potassium. Critically low levels of potassium, during the period of treatment of diabetic acidosis, have also been reported by Martin and Wertmann (9), Nicholson and Branning (10), and Frankel and co-workers (11).

Received for publication March 31, 1949.

* Read by title at the Annual Meeting of the Association for the Study of Internal Secretions, Chicago, June 18–19, 1948.

These studies were furthered by grants-in-aid from the New York Diabetes Association, and the American Medical Association Council on Pharmacy and Chemistry (Grant #538), the interest and cooperation of which are herewith gratefully acknowledged.

† Fellow, The Sadie Baron Wakefield and George P. Wakefield Foundation Memorial Trust Fund.

Our interest in the problem of hypopotassemia in diabetes was aroused by a 37-year-old female diabetic who was admitted to the hospital in severe acidosis. She was treated actively with moderately large doses of insulin and ample fluids. Twelve hours after admission, when the diabetes was coming under control, she showed evidence of paralysis of the diaphragm. Serum potassium was one milliequivalent per liter. She died before a solution of potassium chloride could be administered (12).

Cases such as this one are now being recognized with greater frequency, and help clarify many puzzling situations in diabetic patients where the response is poor in spite of adequate insulin therapy. It is very apparent from many of the complicated situations in a diabetic patient that the adequate treatment of such a person in ketosis and acidosis goes far beyond the therapeutic premise that fluids and insulin are all that is necessary. Many diabetics in coma, whose blood sugar levels, ketosis and acidosis responded well to the usual therapy, have either died or have clinically presented alarming and unexplainable symptoms. It is true that many such deaths are due to a cardiac or some other vascular accident, but it is possible that some are due to profound changes in electrolyte balance.

The present work was undertaken with the idea of obtaining information regarding the frequency with which electrolytic changes occur in the diabetic subject during keto-acidosis[1] before and during therapy with fluids and insulin. Furthermore, it was hoped to arrive at therapeutic indications for the use of electrolytes in a qualitatively and quantitatively specified manner.

SUBJECTS AND METHODS

This study was approached in two ways. The first involved observations during the course of treatment on patients who were admitted to the hospital in diabetic acidosis. Blood and urine specimens were collected at intervals of one to three hours for the determination of serum potassium, sodium, chloride, phosphorus, carbon dioxide combining power, blood sugar, and urinary potassium, sodium, chloride, phosphorus and total nitrogen. The second method of dealing with our problem was to induce ketosis in controlled insulin-treated diabetic patients by reducing or completely stopping insulin administration. After a satisfactory state of ketosis was obtained, oftentimes with acidosis (as evidenced by the presence of large amounts of ketone bodies in the urine, by a significant elevation of blood sugar and by a characteristic fall in the carbon dioxide combining power), the patients were subjected to the diagnostic regimen above de-

[1] The term keto-acidosis is used to indicate the presence of ketone bodies in the blood with a state of acidosis. The purpose is to draw attention to the fact that ketosis may be present without acidosis.

scribed in studying the patients who entered the hospital with severe acidosis. Before and after alteration in insulin dosage, such patients were placed for varying periods of time on a liquid diet of known constitution in regard to chloride, sodium, potassium, carbohydrate, protein, fat and total calories. Insofar as possible, the liquid diets simulated the previously measured diets in all of the above mentioned constituents. Liquid diets were used so that representative aliquots of uniform constituency from the ration for each meal could be sent to the analytical laboratory to determine exactly the amount of sodium, potassium, chloride, carbohydrate, protein and fat present. Thus, we were able to study electrolytic and other balances in the body from hour to hour. When such patients attained ketosis of fairly severe degree, insulin and fluid therapy were started in the same manner as for the patients who were admitted in ketoacidosis.

A considerable mass of chemical data was collected, as determinations were carried out at intervals of from one to three hours before, during and after ketoacidosis in order not to miss any significant alteration in the patient's status.

Serum sodium and potassium were determined by the technic of Overman and Davis using the flame photometer (13), phosphorus by the method of Fiske and Subbarow (14), chloride by the procedure of Wilson and Ball, (15). All values, except those obtained for phosphorus, were converted to milliequivalents per liter. The carbon dioxide combining power estimated by the method of Van Slyke (16), blood sugar by that of Folin and Wu (18), and nonprotein nitrogen and total nitrogen by the micro Kjeldahl procedure (17).

RESULTS

Thirteen patients were followed for electrolytic changes in blood and urine, before and after the institution of therapy for diabetic keto-acidosis. Table 1 contains data referring only to the significant changes in these 13 patients. In 8 of these, none of whom developed coma, ketosis was induced. Five patients were admitted to the hospital for severe diabetic keto-acidosis, 2 of them in coma. In these patients studies of the blood and urine were made while therapy was being carried out. All 13 patients (Table 1) presented a definite fall in the level of potassium in the serum at some time during the period of treatment with insulin. This fall was paralleled in large measure by a fall in serum phosphorus. Three of the 8 patients in whom ketosis was induced showed a fall of serum potassium to critically low levels during the ketotic state, while under treatment. Two of the 5 patients in whom keto-acidosis occurred spontaneously developed a critical fall in serum potassium after the institution of insulin therapy (Cases 8

TABLE 1. SIGNIFICANT CHANGES IN BLOOD CHEMISTRY BEFORE AND AFTER TREATMENT

Case	Age (yrs.)	Color	Sex	No. of hours after insulin	Concentration in blood							Total dosage insulin (units)	Clinical status in keto-acidosis*
					Na	K	Cl	P	Glucose	NPN	CO_2 in vol. %		
					mEq./L				mg./100 ml.				
1	19	W	F	0	139.0	6.40	98.0	—	340	—	10	—	Conscious
V.S.				17½	145.0	4.60	101.5	—	64	—	42	100	
				0	150.0	4.10	90.7	—	228	—	—	—	Conscious
				24	150.0	3.30	102.0	—	466	—	—	47	
2	18	W	M	0	147.0	6.40	105.2	—	428	86	28	0	Conscious
M.B.				17½	144.0	4.10	94.0	3.2	104	—	52	85	
				30	144.0	3.10	95.8	1.8	198	—	58	147	
3	39	W	F	0	150.0	4.10	96.5	—	516	—	—	0	Conscious
S.M.				6	143.5	3.58	98.0	—	384	—	—	50	
4	52	W	M	0	144.0	7.40	85.0	5.8	500	—	21	0	Stuporous
E.B.				23½	150.0	1.80	84.0	3.5	375	—	86	180	
				29½	147.0	1.30	91.0	7.7	208	—	82	180	
				56½	144.0	3.90	85.0	4.9	490	—	49	205	
5	71	W	M	0	147.5	4.35	100.0	4.1	406	55	38	0	Semi-stuporous
E.L.				11½	147.5	3.32	103.0	3.1	28 (shock)	38	—	75	
				22½	143.5	5.38	96.0	2.6	142	—	—	140	
6	47	N	M	0	150.0	7.40	94.0	4.6	290	—	40	0	Conscious
W.C.				12	142.0	3.30	101.0	3.0	143	34	43	100	
				93½	154.0	2.30	102.0	3.5	175	—	54	285	
				118½	150.0	2.10	99.0	3.3	—	—	—	375	
7	46	W	N	0	150.0	3.84	98.4	4.5	470	61	30	0	Semi-stuporous
C.S.				47	142.0	12.30	74.0	—	420	85	15	90	
				67½	154.0	3.30	116.0	2.0	45	70	58	290	
				69½	154.0	2.10	115.0	2.0	15	—	—	—	
8	48	W	M	0	150.0	7.20	87.4	—	407	43	26	—	Stuporous
H.M.				25	154.0	3.10	103.4	2.6	130	28	54	150	
				58	150.0	4.40	105.2	2.6	90	26	58	330	
9	54	W	M	3	143.5	2.10	97.5	3.9	38	—	—	80	Semi-stuporous
M.E.	(PZI 40, 40 units for 48 hrs. preceding admission			27	143.5	3.60	100.0	—	165	—	—	—	
				51	154.0	5.14	105.0	3.0	240	—	—	—	
10	72	W	F	14	—	—	—	—	328	—	28	75	Conscious; febrile
V.C.				22	170.0	3.90	131.6	—	300	—	58	175	
11	71	W	F	0	—	—	—	—	550	—	53	0	Comatose
C.C.				3	159.0	3.30	103.4	—	—	—	—	75	
12	72	W	F	12	159.0	2.30	118.4	2.6	425	120	34	245	Comatose
A.W.				36	164.0	2.60	130.6	—	83	124	38	455	
13	61	W	F	13½	150.0	3.30	103.3	—	204	—	53	60	Semi-stuporous
L.B.				30	150.0	4.90	101.5	—	548	—	—	60	

* In cases 1–8 inclusive, ketosis occurred under controlled conditions, while the patients were in the hospital. Patients 9–13 were admitted in diabetic acidosis. The data contained in this table refer only to the significant changes. The hours at which these occurred are indicated.

and 11; Table 1). Two of the patients with extremely low levels for potassium in serum (Cases 4 and 6; Table 1) presented symptoms commonly ascribed to hypopotassemia; namely, marked weakness and generalized hypotonia. One of these patients (Case 4; Table 1) was treated for the hypopotassemia with Darrow's solution, and a decided improvement in his clinical status was noted. In one patient (Case 7; Table 1) under treatment a marked rise in serum potassium occurred prior to a fall to critical

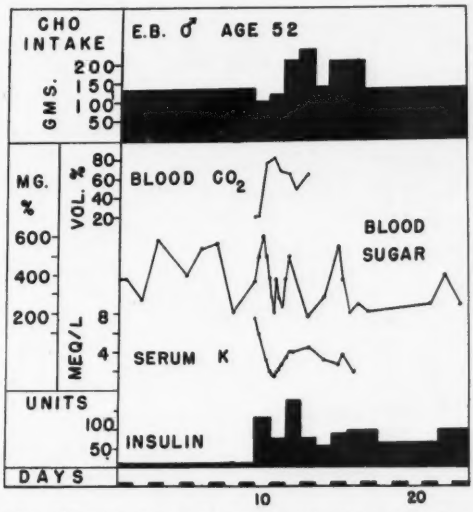


FIG. 1. Relationship of insulin dosage to serum potassium, blood sugar, carbon dioxide combining power and carbohydrate intake in a patient with diabetic acidosis (Case 4; Table 1).

levels. This rise may have been associated with a temporary renal insufficiency.

In general, the fall in serum potassium paralleled the fall in blood sugar. However, the level for blood sugar did not determine the serum potassium level, since in some instances the blood sugar was high with a low serum potassium (Cases 2, 4 and 6; Table 1), and in another instance the blood sugar was at a level usually seen in insulin shock with only slight lowering of the serum potassium (Case 5; Table 1). The relationship of blood sugar, serum potassium and carbon dioxide combining power to insulin and carbohydrate intake is illustrated in Figures 1 and 2. In Figure 1 it will be noted that the serum potassium fell from a level of 7.4 mEq./L to 1.3 mEq./L within twenty-nine and one-half hours after the patient received 180 units of insulin. Dilution of the concentration of potassium in the

serum by expansion of the extracellular fluid accounted for a fall in the serum potassium to 4.1 mEq./L. In Figure 2 it may be seen that the serum potassium fell from 6.4 mEq./L to 3.1 mEq./L within thirty hours after 147 units of insulin had been administered. From balance data it was possible to calculate that the anticipated fall of serum potassium by dilution of extracellular fluid could only account for a drop in serum potassium to 4.6 mEq./L. Thus, in these 2 cases we cannot ascribe the fall in serum potassium to expansion of the extracellular fluid alone.

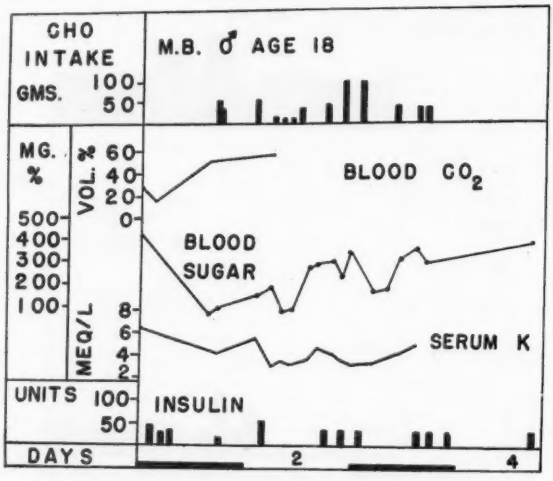


FIG. 2. Relationship of insulin dosage to serum potassium, blood sugar and blood carbon dioxide combining power and carbohydrate intake in a patient with diabetic acidosis (Case 2, Table 1).

Levels for sodium in the serum were moderately high during the keto-acidotic phase in both groups of patients, and were usually not altered materially by insulin therapy. When significant changes did occur, these were of a reciprocal nature with a tendency for sodium levels to rise as potassium levels fell (Cases 1, 4, 6; Table 1). This observation is nicely illustrated in Figure 3, which represents changes in the serum potassium, sodium and chloride, and shows the electrolytic balance in a single patient in whom keto-acidosis was induced by reducing the intake of insulin (Case 7; Table 1). It will be noted that when the potassium rose from 3.6 mEq./L to 12.4 mEq./L (Fig. 3), the sodium fell from 150 mEq./L to 142 mEq./L. Later, when the value for potassium decreased to 2.1 mEq./L, the sodium increased to 154 mEq./L.

Levels for chloride and sodium in the serum were somewhat elevated in

those patients who were admitted to the hospital in diabetic acidosis (Cases 10, 12, 13; Table 1). During treatment with insulin, the level for chloride in all patients tended to move in an opposite direction from the level for potassium. This was most dramatically illustrated in Figure 3 (Case 7, Table 1). It will be noted that within the first forty-eight hours after start-

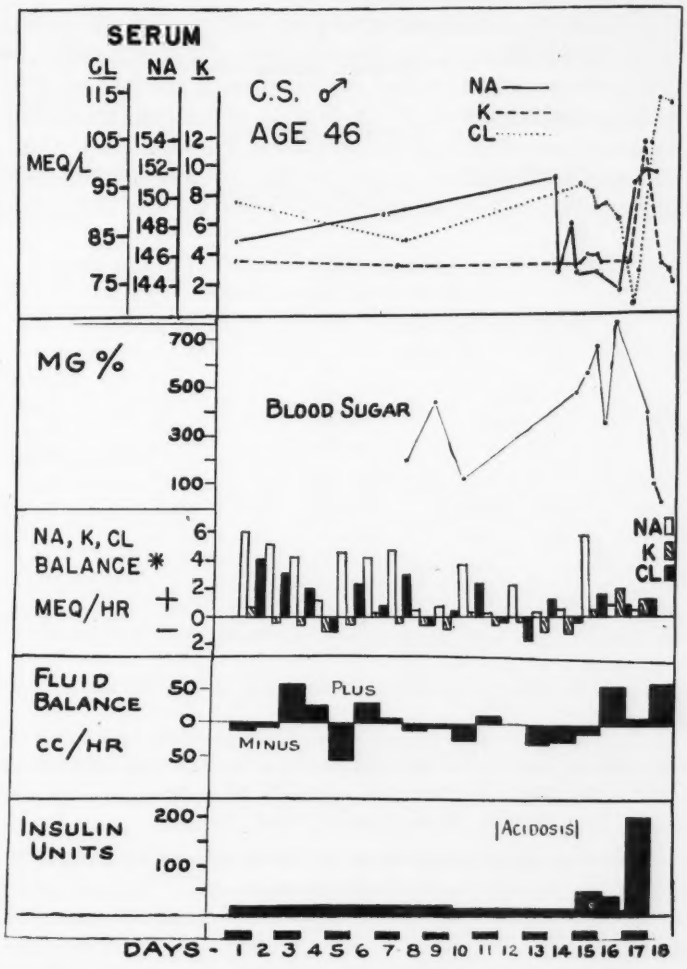


FIG. 3. Relationship of serum electrolytes (chloride, sodium, potassium) to blood sugar, electrolyte balance, fluid balance and daily insulin dosage.

* Balances for sodium, potassium and chloride do not include loss of electrolytes in the feces and perspiration.

ing insulin therapy the serum chloride fell to low levels while the potassium rose abruptly; but within the next twenty-four hours, when the potassium decreased to 2.1 mEq./L the serum chloride increased to 115 mEq./L. In general, the serum chloride fluctuated with the serum sodium. However, the range of fluctuation for chloride was wider, and the inverse relationship to potassium more sharply defined.

Balance studies on a measured intake and output of electrolytes, carried out both before and during the keto-acidotic state, revealed a negative balance for sodium, potassium and chloride during the keto-acidotic state, with a positive balance after the institution of insulin therapy. In other words, the excretion of electrolyte exceeded its ingestion during the uncontrolled diabetic state, but after specific therapy was started the reverse situation prevailed, with a definite diminution in the loss of the substances

TABLE 2. WATER AND ELECTROLYTE BALANCE† IN A DIABETIC TREATED FOR KETO-ACIDOSIS

H.M., age 48, male. Weight—50 Kg.

Water (cc.)	Total intake* 4,425		Total loss** 2,665	Balance +1,760	Electrolyte changes in serum (mEq./L)
Electrolytes (mEq.)	Na	802.0	58.7***	+743.3	150 to 154
	K	0	61.1	+743.3	7.2 to 3.1
	Cl	720.0	47.6	+672.4	87.4 to 103.4

† This study represents the period of time when intensive therapy was started to the time when the maximum fall in serum potassium was obtained. This period of time was twenty-five hours.

* Includes water given intravenously and water from oxidation of administered glucose and lactose.

** Includes loss in urine and insensible loss calculated on the basis of 0.5 cc./Kg./hr.

*** Includes loss in urine and insensible loss. Loss in insensible perspiration was calculated on the assumption that each liter of perspiration contained the following amount of electrolyte: Na—60 mEq., K—5 mEq., Cl—40 mEq.

Calculation of extracellular water by chloride balance (19), (20), (21)

$$E_2 = \frac{E_1 \cdot Cl_1 + b_{cl}}{Cl_2},$$

where

E_1 = Initial extracellular water (20 per cent of body weight)
Cl_1 = Initial concentration of chloride in serum (mEq./L)
b_{cl} = Balance of chloride

Using this formula which assumes that all of the chloride went into extracellular fluid, the latter is increased from a total of 10.0 liters to a total of 14.9 liters.

mentioned. However, the urinary output of sodium, chloride and potassium did not reflect the levels in the serum. The sharp drop in serum potassium, after insulin therapy, coincided with a fall in the urinary output of potassium. As pointed out previously, this drop cannot be accounted for by dilution of extracellular fluid alone, and would indicate a disap-

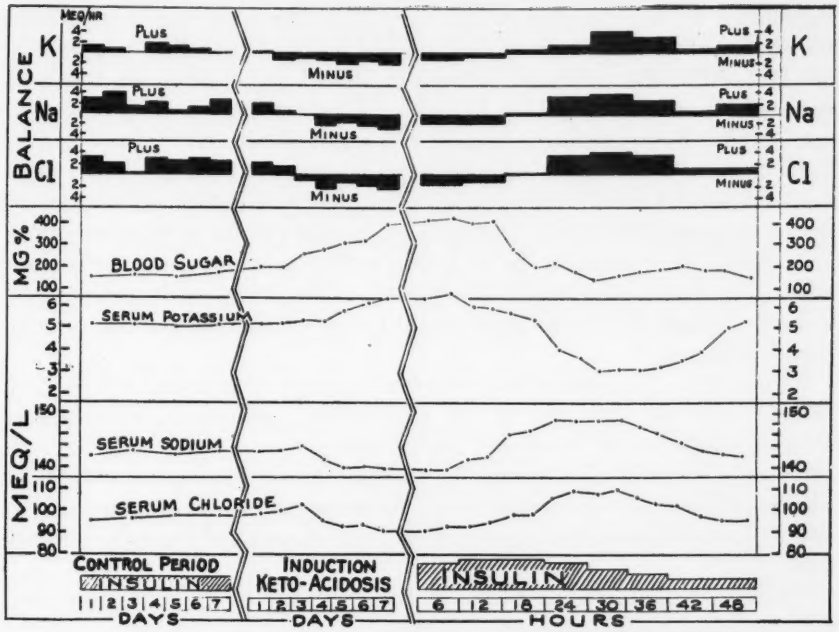


FIG. 4. Schematic graph illustrating electrolyte balance before and after keto-acidosis (conclusions drawn from 13 diabetic subjects).

pearance of potassium from the *serum*, but not its excretion by way of the kidney.

Complete balance of water and electrolytes in one of our cases from the time of inception of intensive therapy for keto-acidosis to the point at which the maximum fall in serum potassium occurred is illustrated in Table 2. During this period of twenty-five hours, an analysis of chloride balance showed an increase in the volume of the extracellular fluid from 10 to 14.9 liters. By this increase in the volume of extracellular fluid we may anticipate a dilution of the potassium in the serum by 2.4 mEq./L or a drop in concentration from 7.2 mEq./L to 4.8 mEq./L. The actual fall in the level of potassium in the serum was to 3.1 mEq./L, which represents a loss of 4.1 mEq./L instead of the anticipated 2.4 mEq./L, or 1.7 mEq./L

above the expected loss by dilution. This amount of 1.7 mEq./L is equivalent to 25 mEq. of potassium lost from the total volume of the extracellular fluid.

The increase in the volume of the extracellular fluid from 10.0 to 14.9 liters is due in part to the intake of 1.8 liters of fluid (as shown by the water balance in Table 2), and indicates that the extracellular volume was augmented by the transfer of 3.1 liters of water from the intracellular compartment. On the basis of the hypothesis that base follows the movement of fluid, 450 mEq. of potassium should have been set free and excreted. In addition to this 25 mEq. of potassium was lost from the extracellular fluid, making a total of 475 mEq. of potassium. As shown in Table 2, there was a negative potassium balance of 61 mEq. which represents the actual amount of potassium lost. Thus, 414 mEq. of potassium cannot be accounted for by excretion or in either of the compartments of body fluid. The conclusion to be drawn is that this amount of potassium must have either migrated to other parts of the body, such as the liver, or been changed to a form which could not be determined by our present chemical means.

Figure 4 is a composite and schematic graph illustrating electrolytic balance and the behavior of the electrolytes, potassium, sodium, and chloride in the serum before and during keto-acidosis, and during the first forty-eight hours of intensive insulin therapy. The crucial period of marked change in the levels for electrolytes in the serum occurred between eighteen and forty-two hours after beginning active treatment of the keto-acidotic state.

Nitrogen balance was negative in the uncontrolled diabetic state, and positive after beginning insulin therapy.

DISCUSSION

In both diabetic ketosis and acidosis the serum potassium falls after treatment with insulin. This indicates the causative mechanism to be the same in the two conditions. The administration of insulin causes a shift of glucose to the hepatic cell. Potassium and phosphate are both involved in this cellular shift, participating in the phosphorylation of glucose and its conversion to glycogen. Usually, the transportation of potassium to the cell causes a transient state of hypopotassemia without symptoms. However, in the patient with diabetic keto-acidosis certain mechanisms are at play which may cause a fall of potassium in the serum and other tissues to critical levels.

Our balance studies for electrolytes show a definite decrease in the urinary output of potassium following the administration of insulin. This is a conserving mechanism, which tends to maintain the serum potassium

at a relatively normal level. In spite of this, serious depletion of serum potassium may occur and indicates its disappearance from the extracellular spaces into the intracellular spaces, since it does not leave externally as shown from balance studies and by a sharp fall in excretion of potassium in the urine.

As a result of severe diuresis, and despite the effort of the kidney to conserve potassium, the diabetic patient frequently loses excessive amounts of both this element and phosphate. This diuresis may continue for some time after therapy with insulin is begun. Thus, the body may be depleted of potassium prior to therapy, and this depletion may become critical in the face of otherwise adequate treatment. In the keto-acidotic state excessive destruction of tissue and vomiting may both contribute still further to the already extreme loss of potassium.

The net result of this steady, long-continued loss of potassium is most strikingly reflected in the status of the muscles, the heart and the neuromuscular junctions. These are the sites involved in the syndrome of hypopotassemia. When potassium is drawn from other tissues to the liver following the administration of insulin to the patient with diabetic keto-acidosis, during the process of glycogenation, a further deficit of potassium occurs at these sites. When this depletion is sufficiently great, symptoms appear. Since the symptoms of hypopotassemia are actually the result of a much lowered concentration of potassium in the muscles, neuromuscular junctions, and heart, the serum concentration of potassium does not necessarily indicate the severity of the process. That is, it may be possible to have the symptoms of hypopotassemia with only a slight reduction in the value for potassium in the serum.

The manifestations of hypopotassemia are readily recognized. However, one must bear in mind the fact that such a syndrome is indeed most frequently observed in diabetic acidosis in relation to active therapy with insulin. The initial symptom is commonly a state of restlessness. This appears in spite of the fact that the blood sugar and ketonuria are decreasing. This restlessness is followed by a generalized hypotonia and apathy with diminution of the deep tendon reflexes. This hypotonic phase may be ushered in without preceding restlessness. In such instances, the patient has usually been admitted to the hospital with severe keto-acidosis.

The most dramatic evidence of hypopotassemia may next make its appearance, that is, diaphragmatic paralysis. Respiratory embarrassment and readily demonstrable anoxemia occur. All the accessory muscles of respiration are then used for pulmonary aeration. The supraclavicular fossae and the intercostal spaces are retracted during the inspiratory phase of respiration, and careful examination will reveal no movement of the diaphragm. Active treatment with potassium is urgently needed at this

time, and will cause rapid disappearance of the diaphragmatic paralysis.

Certain circulatory phenomena have been described (11) as part of the syndrome of hypopotassemia: a) an increased pulse pressure; b) a collapsing pulse; c) an increase in cardiac dullness; d) a systolic murmur, and e) a high venous pressure. These phenomena are directly ascribed to the alterations in the levels for potassium in the serum. We have not been impressed by the specificity of these signs, as hypopotassemia per se certainly produces a shock-like syndrome. All of the manifestations above noted are commonly observed in shock, irrespective of origin.

The electrocardiographic changes found in the syndrome of hypopotassemia are striking (7, and 21–24).

It was pointed out previously that there is no definite serum level of potassium at which symptoms will appear. The lowering of the serum potassium level is merely an indication of what has transpired as the result of potassium loss and potassium mobilization, metaphorically a road over which such processes travel. Hence, the use of the term "hypopotassemia syndrome" is indeed poorly chosen. It seems more accurate to designate the symptom-complex as the "potassium depletion syndrome" (11).

As a result of studies on salt tolerance (unpublished data), it is our belief that fluctuations in potassium in diabetic patients are mediated at least in part through the adrenal and pituitary glands.

In regard to the management of diabetic acidosis, the implications of the above described electrolytic changes are clear cut. Serum potassium should be repeatedly determined while the keto-acidotic diabetic patient is being treated with insulin and fluids. If the value for this element falls to 2 milliequivalents per liter or less, even though no untoward manifestations of deficiency are present, potassium salts should be administered intravenously. However, recognizable symptoms of potassium depletion at higher levels in the serum may fully justify the use of potassium, either by mouth or by infusion. However, a word of caution is necessary whenever potassium is employed therapeutically. Potassium may be toxic if the concentration in the serum is too high (25). In fact the symptoms of hyperpotassemia simulate in some respects those of hypopotassemia. In one of our cases (Case 7; Table 1) the potassium level was so high at one time that administration of potassium would have been dangerous, although later it was needed.

SUMMARY

1. Each of 13 patients with diabetic ketosis or keto-acidosis presented a definite fall in the level of potassium in the serum at some time during the period of treatment with insulin, fluids and the commonly used salts. Three

of 8 patients in whom ketosis was induced and 2 of 5 patients in whom insulin therapy was started immediately after admission to the hospital for diabetic acidosis, showed a diminution in the potassium of the serum to critically low levels. A marked rise in the potassium of the serum occurred in 1 patient prior to a decrease to a dangerously low value.

2. In large measure the decrease in potassium of the serum was paralleled by a similar alteration in serum phosphate.

3. Two of the patients with critically low levels for potassium in the serum presented symptoms of potassium depletion.

4. The fall of serum potassium, during insulin administration, tended to parallel a lowering of blood sugar. However, absolute values for these two substances were not interdependent, as the blood sugar was high in some instances in which a low level for potassium in the serum existed, and in other instances the reverse was true.

5. In all patients during the keto-acidotic phase, levels for sodium and chloride in the serum were rather high. They were not significantly altered by insulin in the majority of subjects. However, in some instances there was a tendency for the sodium and chloride in the serum to rise as the potassium fell.

6. There was a negative balance for sodium, potassium, chloride and nitrogen during the keto-acidotic state, and a positive balance after the institution of insulin therapy.

7. The possible causes, clinical manifestations and therapeutic implications of potassium depletion have been discussed.

REFERENCES

1. Harrop, G. A., Jr., and Benedict, E. M.: The role of phosphate and potassium in carbohydrate metabolism following insulin administration, *Proc. Soc. Exper. Biol. & Med.* **20**: 430, 1923.
2. Briggs, A. P.; Koechig, I.; Doisy, E. A., and Weber, C. J.: Some changes in the composition of blood due to the injection of insulin, *J. Biol. Chem.* **58**: 721, 1923.
3. Atchley, D. W.; Loeb, R. F.; Richards, D. W., Jr.; Benedict, E. N., and Driscoll M. E.: On diabetic acidosis: a detailed study of electrolyte balances following the withdrawal and reestablishment of insulin therapy, *J. Clin. Investigation* **12**: 297, 1933.
4. Elkinton, J. R., and Winkler, A. W.: Transfers of intracellular potassium in experimental dehydration, *J. Clin. Investigation* **23**: 93, 1944.
5. Wiley, F. H., and Wiley, L. L.: The inorganic salt balance during dehydration and recovery, *J. Biol. Chem.* **101**: 83, 1933.
6. Darrow, D. C.: Body-fluid physiology: the relation of tissue composition to problems of water and electrolyte balance, *New England J. Med.* **233**: 91 (July 26) 1945.
7. Bellet, S., and Dyer, W. M.: The electrocardiogram during and after emergence from diabetic coma, *Am. Heart J.* **13**: 72, 1937.
8. Holler, J. W.: Potassium deficiency occurring during the treatment of diabetic acidosis, *J.A.M.A.* **131**: 1186 (Aug. 10), 1946.

9. MARTIN, H. E., and WERTMAN, M.: Serum potassium, magnesium and calcium levels in diabetic acidosis. *J. Clin. Investigation* **26**: 271, 1947.
10. NICHOLSON, W. M., and BRANNING, W. S.: Potassium deficiency in diabetic acidosis, *J.A.M.A.* **134**: 1292 (Aug. 16) 1947.
11. FRENKEL, M.,; GROEN, J., and WILLEBRANDS, A. F.: Low serum potassium level during recovery from diabetic coma, *Arch. Int. Med.* **80**: 728, 1947.
12. LOGSDON, C. S., and McGAVACK, T. H.: Death, probably due to potassium deficiency, following control of diabetic coma, *J. Clin. Endocrinol.* **8**: 658, 1948.
13. OVERMAN, R. R., and DAVIS, A. K.: The application of flame photometry to sodium and potassium determinations in biological fluids, *J. Biol. Chem.* **168**: 641, 1947.
14. FISKE, C. H., and SUBBAROW, Y.: The colorimetric determination of phosphorus *J. Biol. Chem.* **66**: 375, 1925.
15. WILSON, D. W., and BALL, E. G.: A study of the estimation of chloride in blood and serum, *J. Biol. Chem.* **79**: 221, 1928.
16. VAN SLYKE, D. D., and NEILL, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurements: I. *J. Biol. Chem.* **61**: 523, 1924.
17. DREKTER, I. J.; SCISM, R.; HEISLER, A., and STERN, S.: A compact apparatus for the routine distillation of large numbers of samples by the micro Kjehldahl procedure. (To be published).
18. FOLIN, O., and WU, H.: A system of blood analysis, *J. Biol. Chem.* **38**: 81, 1919.
19. STEWART, H. J.; SMITH, J. J., and MILHORAT, A. T.: Electrocardiographic and serum potassium changes in familial periodic paralysis, *Am. J. M. Sc.* **199**: 709, 1940.
20. ELKINTON, J. R., and TAFFEL, M.: Prolonged water deprivation in the dog, *J. Clin. Investigation*, **21**: 787, 1942.
21. GAMBLE, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, ed. 6. Boston, Dept. of Pediatrics, The Harvard Medical School, 1947.
22. PETERS, J. P.: Body Water. The Exchange of Fluids in Man. Springfield, Illinois, Charles C Thomas, Publisher, 1935.
23. BROWN, M. R.; CURRENS, J. H., and MARCHAND, J. F.: Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis, *J.A.M.A.* **124**: 545 (Feb. 26) 1944.
24. SCHERN, D., and BOYD, L. J.: Clinical Electrocardiography, ed. 2. London, William Heinemann, Ltd., 1945.
25. MARTIN, H. E., and WERTMAN, M.: Electrolyte changes and the electrocardiogram in diabetic acidosis, *Am. Heart J.* **34**: 646, 1947.
26. FINCH, C. A.; SAWYER, C. G., and FLYN, J. M.: Clinical syndrome of potassium intoxication, *Am. J. Med.* **1**: 337, 1946.

THE PROGESTERONE THERAPY OF HUMAN UTERINE LEIOMYOMAS

ALBERT SEGALOFF, M.D., JOHN C. WEED, M.D., WILLIAM H. STERNBERG, M.D. AND WILLIAM PARSON, M.D.

From the Departments of Medicine, Gynecology and Pathology of the Tulane University of Louisiana, School of Medicine, the Endocrine Research Laboratories of the Alton Ochsner Medical Foundation, and the Ochsner Clinic, New Orleans, La.

THE experimental production of fibrous tumors of the uterus by Nelson (1) raised the hopes of many clinicians that here was a key to the problem of human leiomyomas. He had succeeded in producing experimental tumors by estrogenic treatment of guinea pigs, and his observations were soon confirmed (2). When Lipschütz (3) announced that the development of this estrogen-induced tumor could be prevented or the tumor made to disappear by the administration of progesterone, it appeared to many that a solution to the problem in humans was at hand. The clinical report of Goodman (4) suggested that the promise of this experimental work had indeed been realized in man. This study was based upon bimanual examination as the means of estimating shrinkage of the uterine tumors.

Lipschütz and co-workers have been studying the experimental tumor intensively. In a recent review of their extensive investigations, they (5) emphasized several aspects of the problem. The fibrous tumors can be elicited by extremely minute quantities of estrogen. The action of the estrogen must, however, be continuous rather than intermittent. If the estrogen is administered in an intermittent or cyclic fashion, even huge amounts fail to induce the development of uterine neoplasms. The experimental fibrous tumors are benign and do not become malignant.

The ability of progesterone to prevent the development of uterine fibromas or to produce their regression is shared by a few other compounds. Furthermore, progesterone is much more potent in its antitumorigenic activity than any of the other compounds which display such activity. The antitumorigenic activity of progesterone is most striking when the administration is by the subcutaneous implantation of compressed pellets of the steroid.

There does not appear to be any correlation between other actions (progestational, androgenic, cortical or anti-estrogenic) of the steroids and their antitumorigenic effectiveness. Moreover, there is no apparent con-

Received for publication April 21, 1949.

nection between the amounts required for antitumorigenesis and any of the other activities. Indeed, it appears that less is required for antitumorigenesis than for the other actions, particularly if the antitumorigenic steroid is administered in the form of compressed pellets.

Clinical application of these experimental studies seems reasonable. This communication represents an attempt to use objective criteria to evaluate the progesterone therapy of human uterine leiomyomas. Six cases are reported. All patients were having regular cyclic bleeding at the onset of therapy. Roentgenograms by means of intra-uterine instillation of radiopaque oil or intraperitoneal insufflation of carbon dioxide were made before and at the conclusion of treatment. Multiple 24-hour urine samples were collected by all patients. Repeated endometrial and breast biopsies were done in certain instances. All patients were subjected to laparotomy and hysterectomy immediately after cessation of progesterone therapy.

The urinary excretion of gonad-stimulating hormone was measured by the method of Klinefelter and associates (6). The 17-ketosteroids were measured by a modification of the Zimmermann reaction, as suggested by Glendenning (7). Dehydro-iso-androsterone was employed as a standard.

Progesterone was given by two methods: either as a daily intramuscular injection of 20 milligrams in peanut oil, or in the form of 200 milligram compressed pellets implanted in the fatty tissue below the scapula.

CASE REPORTS

Case 1.—*B.S.*, a 35-year-old Negro woman (O. C. No. 8895) was found to have a uterus enlarged to about the size of a 3-months' pregnancy. Roentgenograms following the intraperitoneal injection of carbon dioxide failed to show any well-defined mass, but films following the intra-uterine injection of iodized oil (Fig. 1A) showed a sharply outlined tumor protruding into the uterine cavity. Urine collections were made for hormonal assay and daily intramuscular injections of 20 mg. of progesterone in peanut oil were begun. Therapy was continued for sixty days. Figure 2 contains a summary of the course and assay results. At the conclusion of the course of progesterone, roentgenograms taken following intra-uterine injection of oil failed to show any change in the tumor (Fig. 1B). It is of interest to note that after bimanual examination it was our impression that the uterus had definitely decreased in size, but this was not borne out by roentgenography. As can be seen in Figure 2, which summarizes the laboratory data, there was no apparent effect of the progesterone on the course of the regular cycles of uterine bleeding. The urinary gonad-stimulating hormone was not significantly affected nor was the patient's weight. The drop in 17-ketosteroid excretion may or may not be significant, particularly in view of the single pretreatment ketosteroid excretion rate which was obtained. We were unsuccessful in obtaining a biopsy specimen of endometrial tissue which was adequate for diagnosis.

A photograph of the gross specimen is shown in Figure 3. The leiomyomas showed a varied microscopic picture. Some were extremely cellular with a moderate number of mitotic figures; others showed hyaline degeneration, whereas one showed hemorrhagic infarction. The endometrium was moderately atrophic with sparse, small, nonsecretory

ff. "The progesterone was supplied by Ciba Pharmaceutical Products, Inc. through the courtesy of Dr. Ernst Oppenheimer.

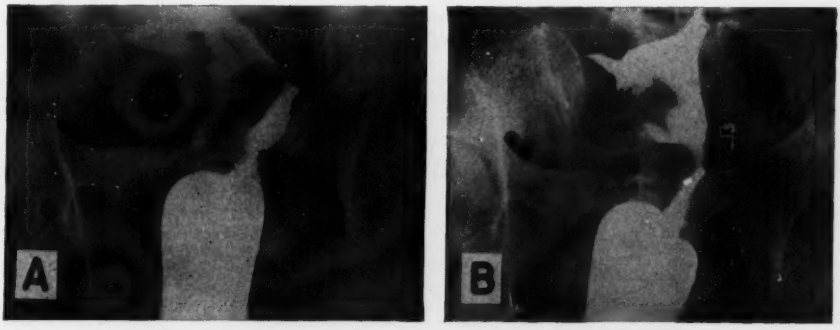


FIG. 1. (Case 1, B. S.) Roentgenograms following intra-uterine iodized oil: (A) before progesterone therapy; (B) after 52 days of progesterone therapy.

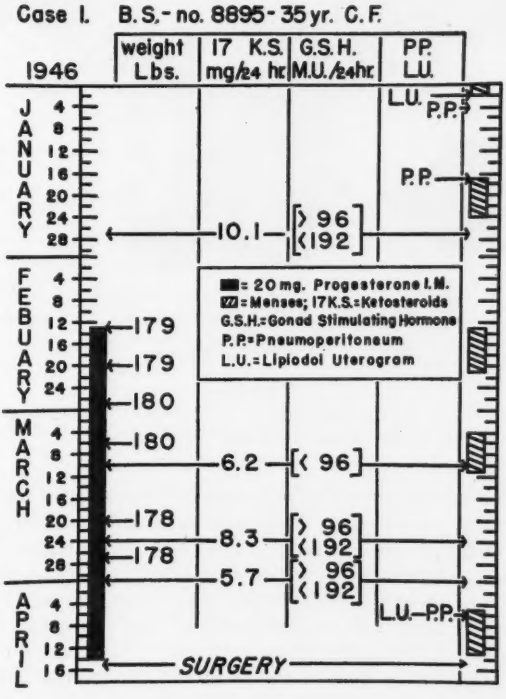


FIG. 2. (Case 1, B. S.) Chart showing therapy, assay results and bleeding.

glands for the most part. Occasional glands suggested an exhausted secretory effect. The stroma was edematous and contained numerous dilated venous spaces. There was squamous metaplasia of the endocervix.

Case 2.—*B. J.*, a 43-year-old Negro woman (C. H. No. T45-195492) gave a long history of abdominal masses which could readily be felt through the abdominal wall. Pneumoperitoneum following injection of carbon dioxide revealed a large mass, many parts of which were calcified. The patient was given daily intramuscular injections of 20 mg. of

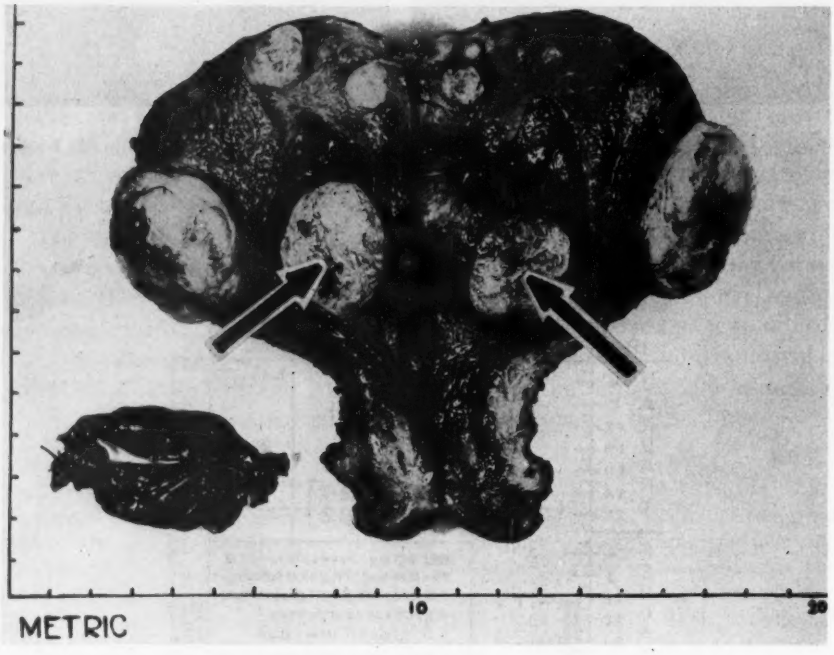


FIG. 3. (Case 1, B. S.) Photograph of excised uterus. Arrows point to the leiomyoma visualized in Figure 1.

progesterone for forty-seven days. Figure 4 contains a summary of the course and assay results. Unfortunately, only a single 17-ketosteroid determination was obtained before treatment and a single one during therapy. The latter determination was considerably less than the former, an observation of doubtful significance, since the creatinine level was also considerably lower in this specimen than in the previous one. Only a single gonadotropic hormone assay was obtained and that was before therapy. It was below the normal limits for our laboratory. Here again, the roentgenogram following pneumoperitoneum after progesterone therapy was essentially the same as that before therapy.

The biopsy specimen obtained from the breast before therapy showed ducts and lobules. The one obtained at operation showed ductal development with proliferation of lobules similar to the breast seen in early pregnancy. In the surgical specimen, the endometrium was rather atrophic but showed no secretory effect. The fibroids showed

considerable hyaline change; there was chronic cervicitis and the ovaries were somewhat fibrotic, with numerous corpora albicantia and few ova or developing follicles, although one ovary contained a theca lutein cyst.

It should be particularly noted that during the period of progesterone administration there was prolonged, daily spotting but no definite menstrual bleeding.

Case 3.—*J. D.*, a 47-year-old white woman (O. C. No. 43074) complained chiefly of recent excessive menstrual bleeding with passage of clots. Bimanual examination revealed a definitely enlarged uterus, and a 4 cm. globular mass could be palpated on its

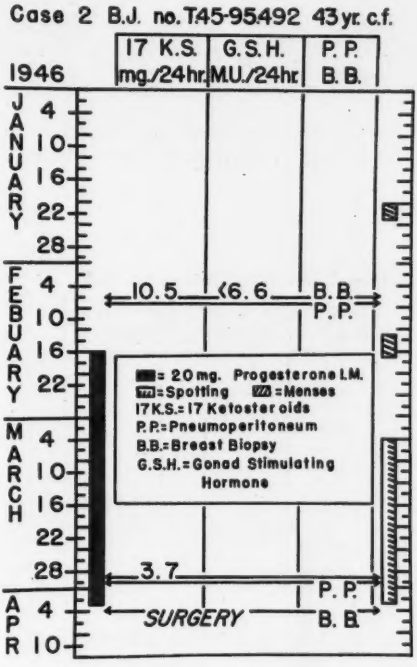


FIG. 4. (Case 2, B. J.) Chart showing therapy, assay results and bleeding.

surface. Carbon dioxide contrast roentgenograms (Fig. 5A) demonstrated this sharply outlined mass. Daily injections of 20 mg. of progesterone were given for thirty-nine days. The course and assays are shown in Figure 6. The 17-ketosteroid determinations, which ranged from 7.3 to 11 mg. in twenty-four hours apparently were not significantly affected by the administration of progesterone. The contrast roentgenograms (Fig. 5B), obtained after the course of progesterone, showed no diminution in size of the tumor. The surgical specimen, illustrated in Figure 7, contained a single, large, solitary leiomyoma. During progesterone therapy the patient noticed a decrease in cyclic bleeding. It is of interest to note that the biopsy specimen of endometrial tissue obtained during bleeding in February before initiation of progesterone therapy revealed a normal secretory endometrium, but the endometrium in the specimen obtained at operation was completely atrophic. The endometrial glands were small and sparse although there was dilatation of

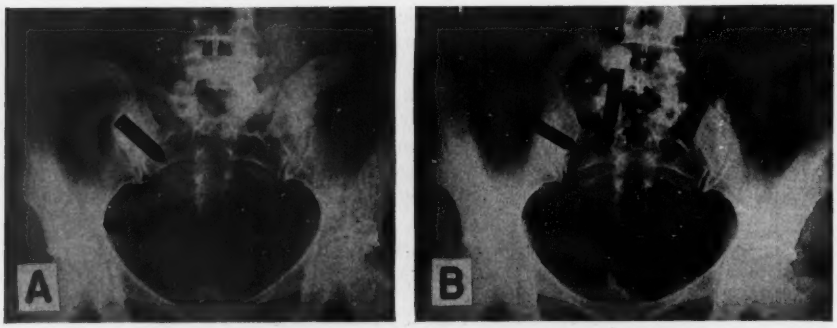


FIG. 5. (Case 3, J. D.) Roentgenograms following intraperitoneal carbon dioxide: (A) before progesterone therapy; (B) after 38 days of progesterone therapy.

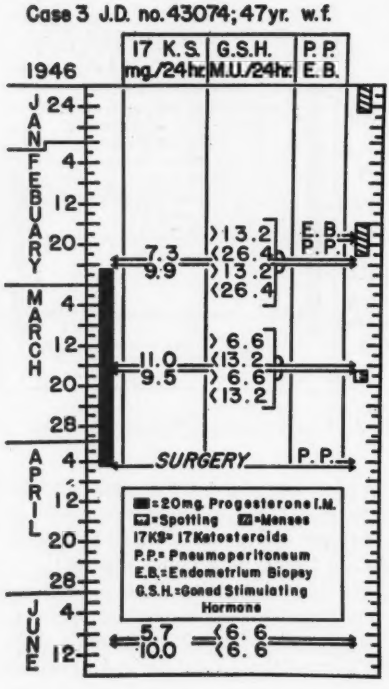


FIG. 6. (Case 3, J. D.) Chart showing therapy, assay results and bleeding.

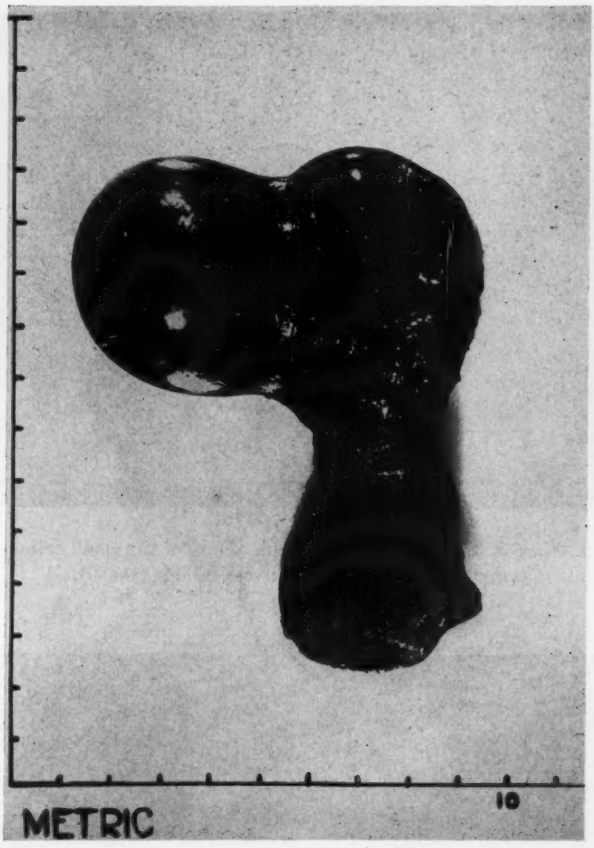


FIG. 7. (Case 3, J. D.) Photograph of uterus containing single, large, solitary leiomyoma.

occasional glands with flattening of the epithelium. The epithelium and stroma showed no secretory effect. The leiomyoma in the surgical specimen showed areas of hyalinization interspersed with areas of increased cellularity, containing numerous smooth muscle cells, with minimal fibrous stroma, and a fair number of mitotic figures. Numerous minute leiomyomas, cellular in character, were seen microscopically. These contained two to four mitotic figures per high power field in some areas (Figs. 8 and 9) and were clearly actively growing early tumors.

Case 4.—*O. F.*, a 36-year-old Negro woman (C. H. No. T46-228266) had a readily palpable pelvic mass; contrast roentgenograms showed a fairly well localized lesion (Fig. 10A). After preliminary breast biopsy and urine collections for hormonal studies, 8 pellets of progesterone, totaling 1627 mg., were implanted below the right scapula. There was some irregularity in the menses during the time the pellets were in place as

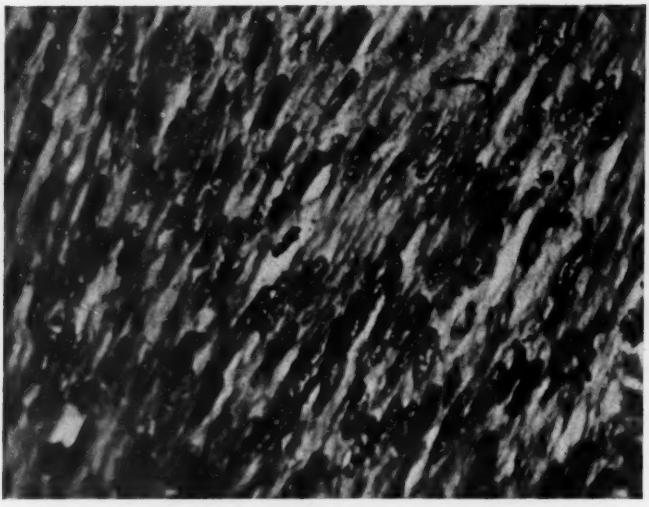


FIG. 8. (Case 3, J. D.) Photomicrograph of one of the small cellular leiomyomas showing four mitoses in field (×480).

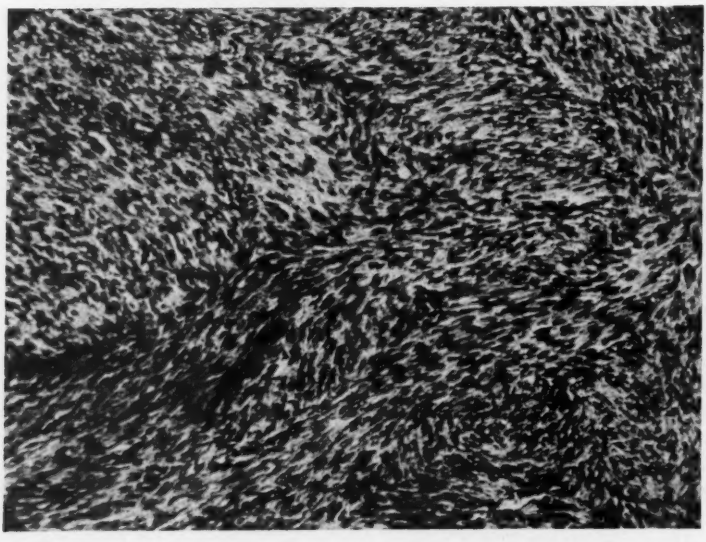


FIG. 9. (Case 3, J. D.) Photomicrograph of another leiomyoma showing degree of cellularity (×130).

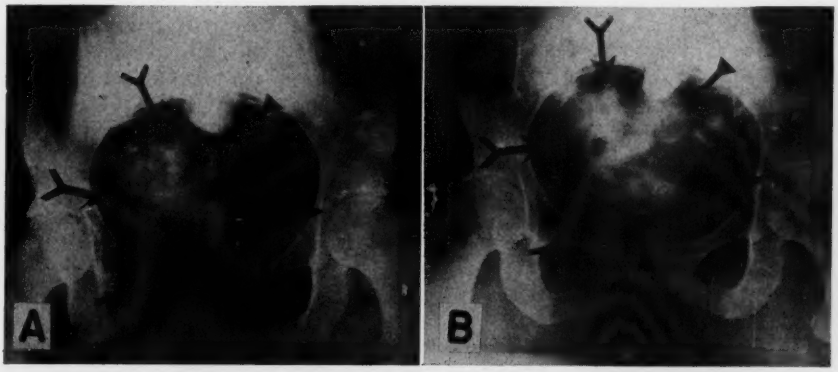


FIG. 10. (Case 4, O. F.) Roentgenograms following intraperitoneal insufflation carbon dioxide: (A) before progesterone therapy; (B) after 189 days of progesterone therapy.

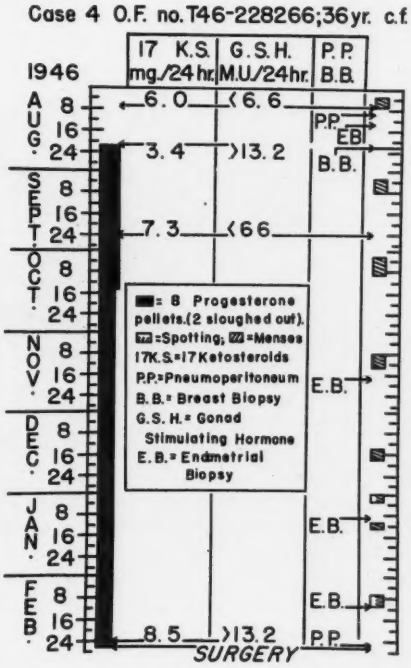


FIG. 11. (Case 4, O. F.) Chart showing therapy, assay results and bleeding.

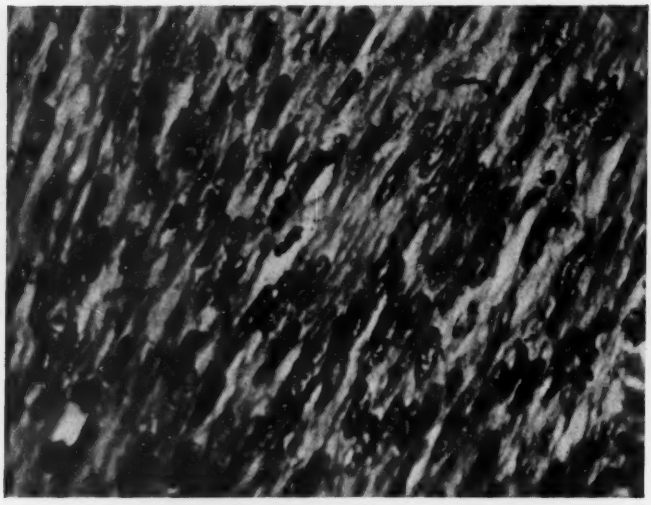


FIG. 8. (Case 3, J. D.) Photomicrograph of one of the small cellular leiomyomas showing four mitoses in field (×480).

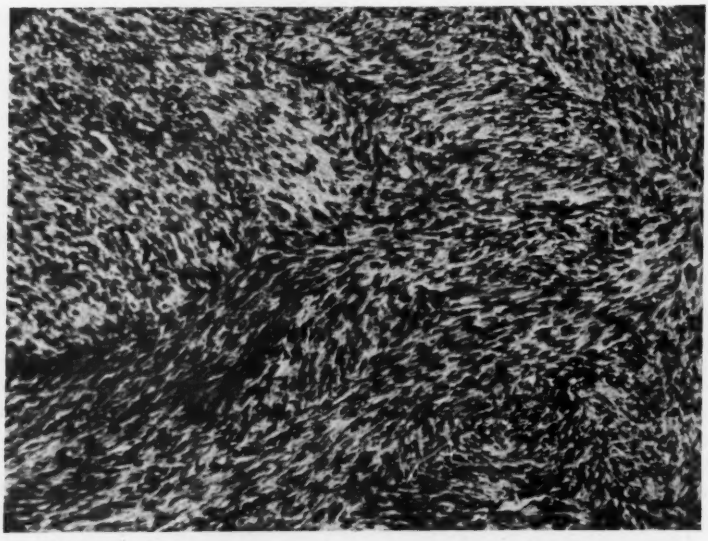


FIG. 9. (Case 3, J. D.) Photomicrograph of another leiomyoma showing degree of cellularity (×130).

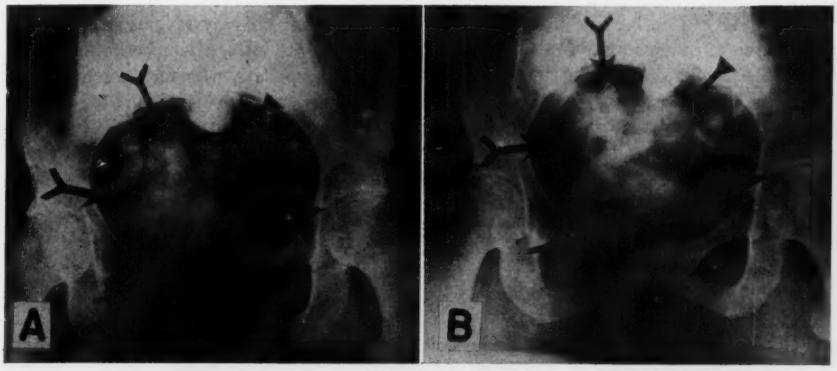


FIG. 10. (Case 4, O. F.) Roentgenograms following intraperitoneal insufflation carbon dioxide: (A) before progesterone therapy; (B) after 189 days of progesterone therapy.

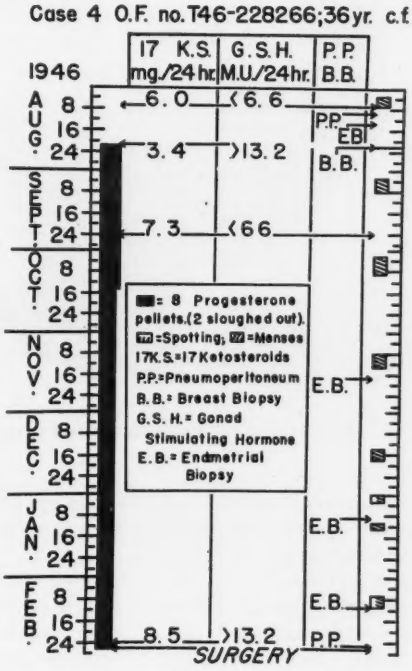


FIG. 11. (Case 4, O. F.) Chart showing therapy, assay results and bleeding.

indicated in Figure 11. Endometrial tissue was obtained for biopsy several times during the course of progesterone therapy. Approximately two months after the implantation of pellets, 2 of them sloughed out. From the remaining pellets, which were removed at the time of operation, we were able to calculate an average absorption of 0.7 mg. of progesterone per pellet per day. Here, again, there was no significant effect on either the excretion of 17-ketosteroids or gonad-stimulating hormones (Fig. 11). However, a single assay of gonadotropic hormone in the early stages of progesterone therapy gave somewhat higher results than in the other two assays, which gave values that were below our

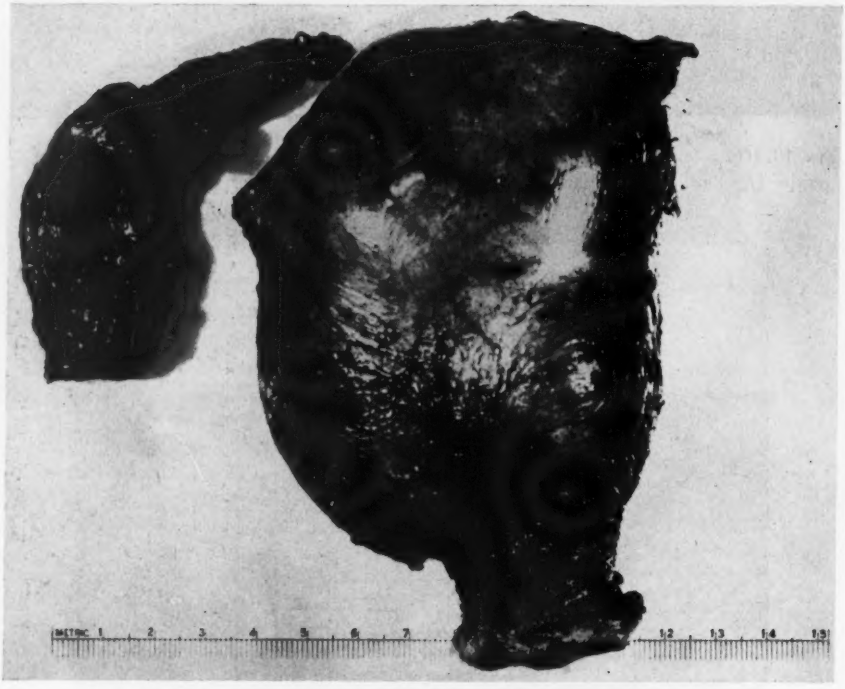


FIG. 12. (Case 4, O. F.) Photograph of excised uterus.

usual normal limits. The six-months' course of progesterone had little or no effect on the size of the leiomyoma, as can be seen from the contrast roentgenograms shown in Figure 10B. The gross surgical specimen is seen in Figure 12.

Little endometrial tissue was obtained for biopsy, but that obtained on February 11, after five months of progesterone treatment, showed definite secretory glands. The surgical specimen also had a fairly well-developed secretory endometrium, although the glands were somewhat sparse. There were multiple leiomyomas, with many active cellular areas and a few hyalinized areas. The cervix was chronically inflamed and the ovary contained numerous ova with several small follicular cysts. Progesterone apparently affected the cycles of bleeding, in that irregularities with periods of spotting occurred.

Case 5.—*E. M.*, a 34-year-old Negro woman (C. H. No. T46-230533) complained of increasing dysmenorrhea and irregularity of bleeding. The uterus was definitely enlarged and after roentgenographic studies with carbon dioxide intraperitoneally, 8 progesterone pellets totaling 1614 mg. were implanted (Fig. 13). The pellets remained *in situ* for 105 days. Preliminary dilatation and curettage demonstrated a well-developed secretory endometrium (Fig. 14). A biopsy specimen taken on the thirteenth day of the following cycle and six days after the onset of progesterone therapy, showed an early secretory effect (Fig. 15). Another biopsy specimen taken shortly before the date of the next expected menstrual period revealed a well-developed secretory effect but some dilatation of glands (Fig. 16). Eight days later, another biopsy specimen, taken while the patient was still bleeding, showed a pseudodecidual reaction and dilated glands with flattened epithelium (Fig. 17). A biopsy specimen taken on the twenty-first day of the following cycle showed further evidence of an exhausted secretory effect, with dilated and collapsed glands, and flattened and somewhat atrophic epithelium (Fig. 18). One month later and shortly before a period of prolonged bleeding the biopsy specimen consisted of atrophic endometrium with sparse, small glands and edema of the stroma (Fig. 19) although the patient at this time had been receiving progesterone for sixty-eight days. The endometrium obtained at operation was completely atrophic (Fig. 20). The leiomyomas were cellular but also showed small areas of hyalinization. There was an old healed salpingitis and the ovary appeared microscopically normal. The contrast roentgenograms taken before and after operation showed no change in the size of the fibroids. The continued uterine bleeding was severe enough to warrant operation before the elected time. The breast biopsy specimen, secured at operation after progesterone therapy, showed pronounced lobular formation and proliferation comparable to the changes seen in early pregnancy (Fig. 21). In contrast the breast biopsy specimen taken before progesterone therapy showed a resting stage (Fig. 22).

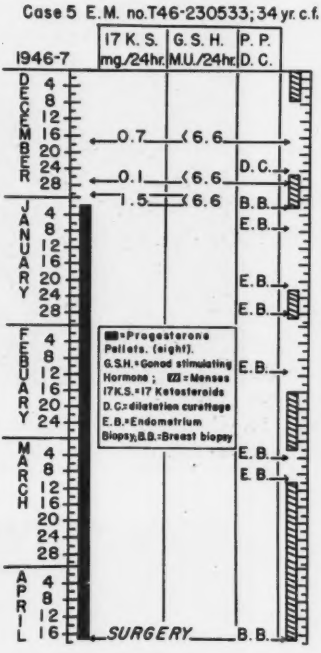


FIG. 13. (Case 5, E. M.) Chart showing therapy, assay results and bleeding.

Case 6.—*V. L. R.*, a 35-year-old Negro woman (C. H. No. T47-248820) was first seen with a chief complaint of increasing dysmenorrhea. The uterus, which was about the size of a 3-months' pregnancy, contained multiple fibroids. Our usual studies were undertaken. There was no gonadotropic hormone in the urine at any time during these studies (Fig. 23). Pneumoperitoneum was induced and 7 pellets of progesterone totaling 1438 mg. were implanted in the subcutaneous tissue. Numerous endometrial specimens were obtained for biopsy. The pellets were removed and an additional biopsy specimen from the breast was obtained. Pneumoperitoneum was again induced prior to operation, and it was noted in the roentgenograms that there was no change in the uterus. Here, as previously, the endometrium initially showed pronounced secretory activity which gradually became exhausted. At operation the endometrium was thin. The glands were atrophic

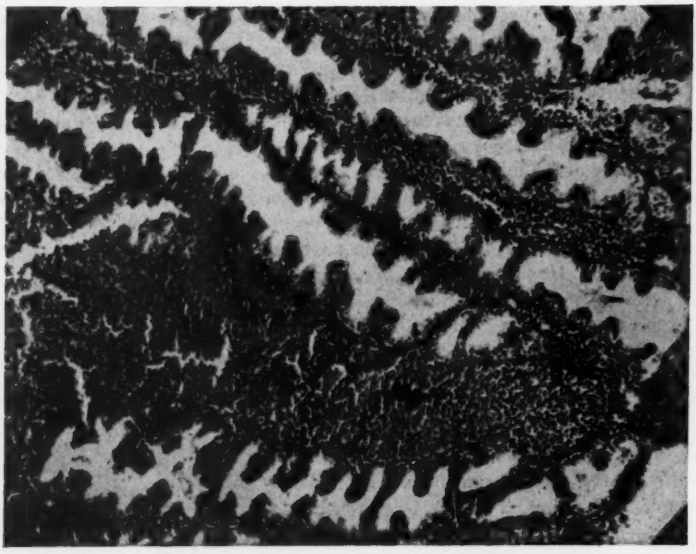


FIG. 14. (Case 5, E. M.) Specimen obtained by curettage on twenty-fourth day of cycle, previous to progesterone therapy, showing well-developed secretory phase (×100).

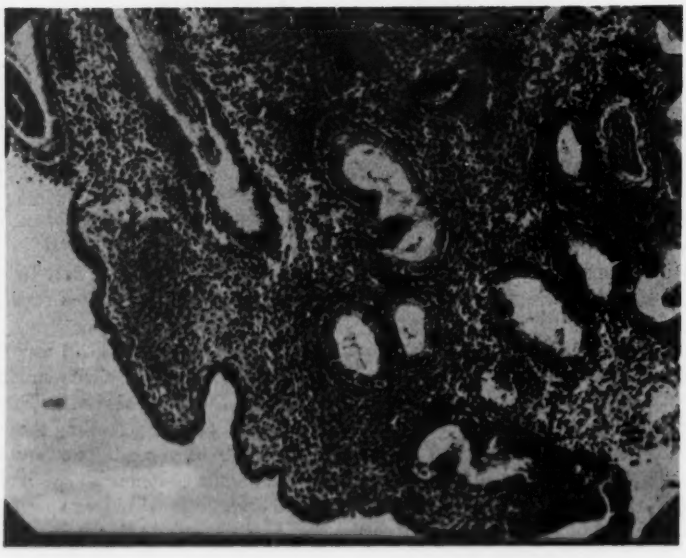


FIG. 15. (Case 5, E. M.) Biopsy specimen of endometrial tissue obtained on thirteenth day of cycle and 6 days after institution of progesterone therapy, showing early secretory effect (×100).

FIG. 16. (Case 5, E. M.) Biopsy specimen of endometrial tissue obtained shortly before date of expected menstruation, and 18 days after onset of progesterone therapy, showing well-developed secretory phase but with some dilatation of glands (×100).

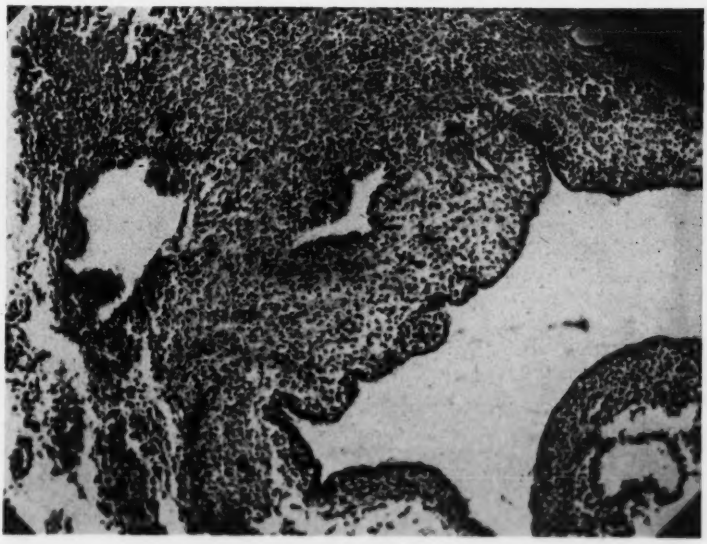


FIG. 17. (Case 5, E. M.) Biopsy specimen of endometrial tissue obtained 8 days after previous biopsy. There is a well developed pseudodecidual reaction but the glands are dilated and the glandular epithelium is flattened (×100).

FIG. 18. (Case 5, E. M.) Biopsy specimen of endometrial tissue obtained on twenty-first day of cycle, and 41 days after start of progesterone therapy, showing exhausted secretory effect, dilated and collapsed glands, flattening and some atrophy of glandular epithelium (×100).

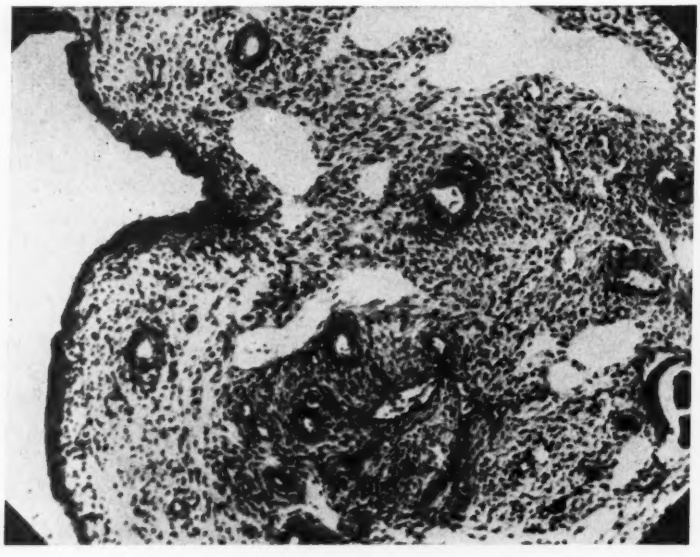


FIG. 19. (Case 5, E. M.) Biopsy specimen of endometrial tissue obtained one month later, and 68 days after start of progesterone therapy, showing atrophic endometrium with sparse, small glands, edema of stroma and dilated venous spaces (×100).

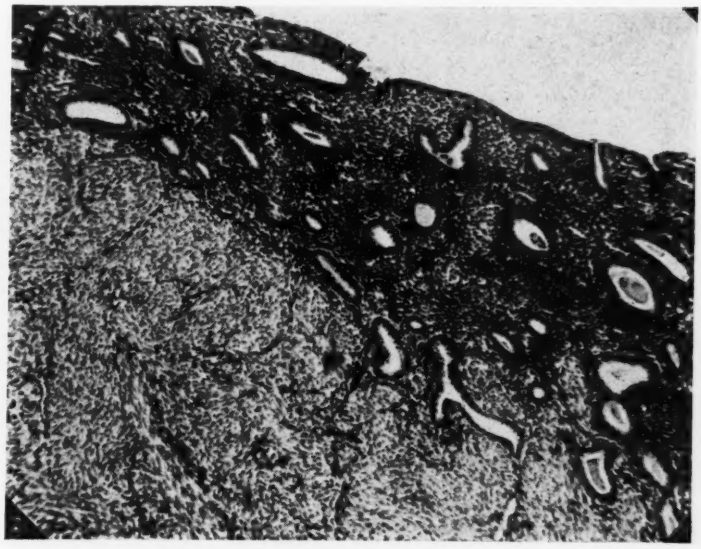


FIG. 20. (Case 5, E. M.) Endometrium from surgical specimen showing considerable atrophy and absence of secretory effect (×100).

FIG. 21. (Case 5, E. M.) Biopsy specimen of breast tissue obtained before progesterone therapy, showing resting stage (×100).

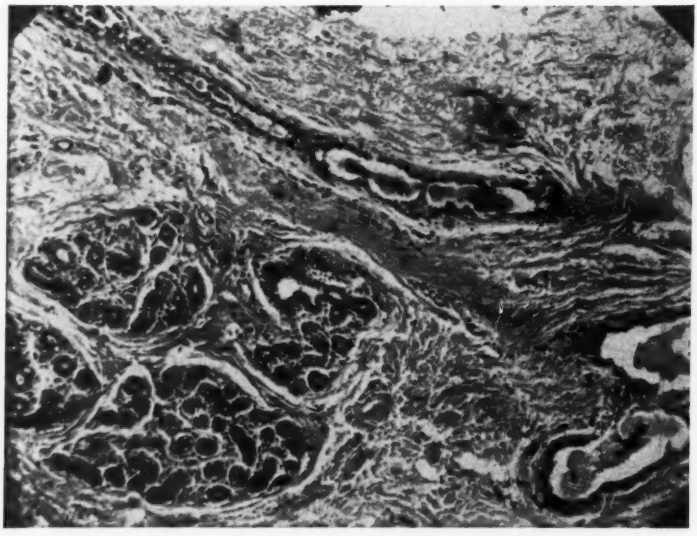


FIG. 22. (Case 5, E. M.) Biopsy specimen of breast tissue obtained after 105 days of progesterone therapy, showing proliferation of epithelium and lobule formation comparable to the changes of early pregnancy (×100).

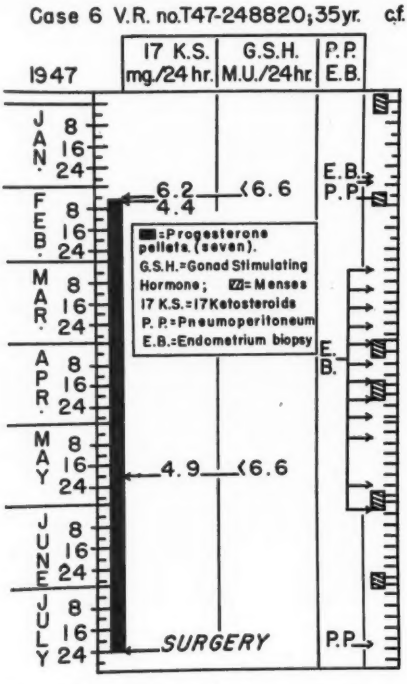


FIG. 23. (Case 6, V. L. R.) Chart showing therapy, assay results and bleeding.

except in small areas where they had the collapsed appearance of an exhausted secretory effect. The superficial endometrial stroma retained some secretory effect. There was no significant change in the urinary excretion of 17-ketosteroids. No effect of the progesterone on the cycles of bleeding was apparent.[1]

DISCUSSION

The major purpose of this study was to attempt to demonstrate by reasonably objective methods any change in the size of leiomyomas of the uterus during progesterone therapy. No alteration in the size of the leiomyomas could be demonstrated in any of the 6 patients treated. Furthermore, there was no microscopic evidence which could be interpreted as an increase in the process of involution in the leiomyomas. Several leiomyomas did show hyaline degeneration but the incidence and degree appeared no greater than would be seen in an equivalent number of untreated tumors. If anything, the degree of cellularity and mitotic activity in many was greater than is usually found in a random sampling of leiomyomas. This was particularly conspicuous in 2 patients in whom numerous, minute (less than 0.5 cm.), highly cellular leiomyomas were present. It is hardly likely that these changes would accompany a limitation or decrease in growth.

The other observations made on these patients are of considerable interest. There appeared to be no consistent effect on the phases of bleeding; in 1 patient there was a decrease, in 2 there was an increase in frequency and amount, and in the other 3 there was no significant change in the cyclic bleeding.

The development of atrophy of the endometrium in 5 of the 6 patients under prolonged therapy with progesterone is worthy of comment. The gradual exhaustion of progestational effect with subsequent atrophy of the endometrium is illustrated in cases 5 and 6, in which frequent endometrial specimens were taken for biopsy. Since progesterone requires an estrogen-primed substrate on which to act effectively, it may be that the failure to elevate the estrogen concomitantly resulted in gradual deterioration of the progestational response.

No consistent effect of progesterone on urinary excretion of 17-ketosteroids was apparent.

It is of considerable interest that in 3 of the 6 patients, gonadotropic hormone could not be demonstrated in the urine by our usual assay procedures either prior to, or during therapy. Similar results have been noted in a much larger group of patients with leiomyomas studied in the course

[1] Of interest is the presence of an active corpus luteum in one of the ovaries removed surgically, indicating no interference with ovulation despite constant progesterone therapy for several months.

of our other work. This may possibly be of significance in the pathogenesis of leiomyomas.

The estimation of changes in the size of uterine masses by pelvic examination is, we believe, an inexact technic subject to considerable error. Clinical studies in which dramatic results have been reported following treatment of leiomyomas with progesterone must be accepted with reserve. It might be pointed out that in Case 1 we ourselves were convinced on bimanual examination that the uterus had shrunk substantially, but the contrast roentgenograms did not bear this out. It is possible that the progesterone may have reduced pelvic congestion or caused some similar result with consequent movement of the uterus deeper into the pelvis, and apparent decrease in the size of the mass.

Testosterone, another tumorigenic compound as indicated by Lipschütz's studies in guinea pigs, has also been used in the treatment of human leiomyomas. In a recent clinical study Vargas and associates (8) reported favorable results with this androgen. They attempted to outline the enlarged uterus with wires on the abdominal wall, followed by roentgenograms. We have made no studies with androgen comparable to those with progesterone, but we would anticipate no better results. We have, incidentally, observed 3 patients with definitely masculinizing syndromes all of whom had large leiomyomas, and a similar case was also noted in the literature.

The failure of response of human uterine leiomyomas to progesterone suggests that these tumors may not be analogous to the experimentally induced guinea-pig tumors. There are other dissimilarities which further reinforce this idea. The guinea-pig tumors are not limited to the uterus or its associated structures but develop in any portion of the abdominal cavity, particularly the uterus, the intestines and the spleen. In contrast, the human tumors develop from the uterus or other associated Müllerian structures, such as the uterine ligaments. Leiomyomas of the gastro-intestinal tract of substantial size are uncommon and when present are not especially associated with uterine tumors. Furthermore, there are notable histologic differences. The guinea-pig tumors are fibromatous proliferations which may incorporate occasional smooth muscle fibers. Even in small tumors, the fibromatous pattern is characteristic. In contrast, the human leiomyoma is specifically a tumor of smooth muscle. Its fibrous component represents the stroma of the tumor, not part of the neoplasm *per se*. This is exemplified in the earliest leiomyomas, which are miliary bundles of immature smooth muscle cells. As the tumor ages and degenerative changes occur, the fibrous stroma becomes more prominent. Pure fibromatous nodules do not develop in them. They are, therefore, as Schiller (10) pointed out, correctly designated as leiomyomas not fibromyomas.

SUMMARY

1. Six patients with uterine leiomyomas were treated with progesterone for periods varying from 30 to 189 days. It was administered to 3 patients in the form of 20 mg. daily, and to the remaining 3 by implantation of multiple compressed pellets. This treatment did not affect the size of the uterine tumors, as demonstrated by contrast radiography.

2. No significant effect of the therapy on the urinary excretion of 17-ketosteroids or of gonad-stimulating hormones was observed.

3. The expected stimulation of the breast tissue was found in the patients in whom such specimens were obtained for biopsy.

4. In 5 patients there was gradual exhaustion of the progestational reaction of the endometrium, until at operation the endometrium showed pronounced atrophy.

5. There was no microscopic evidence of increased involution in the leiomyomas removed at operation. Many, in fact, showed considerable cellularity in their histologic structure.

REFERENCES

1. Nelson, W. O.: Endometrial and myometrial changes, including fibromyomatous nodules, induced in the uterus of the guinea pig by the prolonged administration of oestrogenic hormone, *Anat. Rec.* **68:** 99–102 (April 25) 1937.
2. Lipschütz, A., and Iglesias, R.: Multiples tumeurs utérines et extragénitales provoquées par le benzoate d'oestradiol, *Compt. rend. Soc. de biol.* **129:** 519–524, 1938.
3. Lipschütz, A.; Murillo, R., and Vargas, L., Jr.: Antitumorigenic action of progesterone, *Lancet* **2:** 420–421 (Aug. 19) 1939.
4. Goodman, A. L.: Progesterone therapy in uterine fibromyoma, *J. Clin. Endocrinol.* **6:** 402–408 (May) 1946.
5. Lipschütz, A.: New experimental aspects of the antitumorigenic action of steroid hormones, *Texas Rep. Biol. & Med.* **6:** 3–20 (Spring) 1948.
6. Klinefelter, H. F., Jr.; Albright, F., and Griswold, G. C.: Experience with a quantitative test for normal or decreased amounts of follicle stimulating hormone in the urine in endocrinological diagnosis, *J. Clin. Endocrinol.* **3:** 529–544 (Oct.) 1943.
7. Glendenning, M. B.: Personal communication.
8. Vargas, Fernandez, L.; Vargas, Molinare, R., and Ossandon, G. M.: Disminución de tamaño del fibromioma uterino y supresión de su metrorragia por la implantación subcutánea de testosterona, *Rev. méd. de Chile* **73:** 443–445 (May) 1945.
9. Williams, G. A., and Mendenhall, W. A.: Adrenal-like masculinizing tumor of the ovary associated with bleeding fibromyoma uteri, *Am. J. Obst. & Gynec.* **53:** 525–528 (March) 1947.
10. Schiller, W.: The Female Genitalia, *in* Pathology edited by Anderson, W. A. D., St. Louis, C. V. Mosby Co., 1948, p. 1154.

SERUM PRECIPITABLE IODINE IN PATIENTS WITH TUMORS OF OR NEAR THE PITUITARY*

J. P. PETERS, M.D., W. J. GERMAN, M.D.
AND E. B. MAN, PH.D.

From the Departments of Internal Medicine and Neurosurgery, Yale University School of Medicine, New Haven, Connecticut

IN AN earlier paper (1) it was pointed out that, in a number of patients with tumors of or in the vicinity of the pituitary gland, the concentrations of precipitable iodine in the serum (SPI) were as low as they usually are in myxedema, although clinical evidences of hypothyroidism were lacking. Since that time a larger number of such patients has been studied and the investigation has been extended to include an assessment of other endocrine functions.

MATERIAL AND METHOD

Altogether 20 patients have been studied. With one exception they were at some time or another on the Neurosurgical Service; many were at times on the Metabolism Service of the Department of Internal Medicine. All but the last, Case 20, were examined and assessed by both services. The diagnoses were made from history, physical findings, laboratory data and x-ray examinations. In 7 cases they were verified by operation, and in 1 by postmortem examination as well.

In all but 2, SPI was measured on one or more occasions. In these 2, such measurements were useless because in Case 12 the patient had recently received Priodax and in Case 13 had been injected with Diodrast to obtain an arteriogram before blood had been drawn for SPI. In 8 cases basal metabolism was also measured. Serum lipids were determined at least once, in 17 patients. In 13, adrenocortical function was assessed by analyses of the serum for electrolytes and in 15, by measurements of blood sugar. In 10 patients, 5-hour glucose tolerance tests and in 9, salt-restriction tests were carried out. Gonadal function was evaluated from history and physical examinations and, in male subjects, by measurement of urinary 17-ketosteroids.[1]

SPI was measured by the method of Riggs and Man (2), lipids by the methods of Man *et al.* (3, 4, 5, 6, 7), sodium and potassium by the methods

Received for publication May 2, 1949.

* Aided by a Grant from the U. S. Public Health Service.

[1] For these measurements we are indebted to Dr. Frances D. Humm of the Department of Pharmacology.

TABLE 1. LABORATORY DATA AND TREATMENT OF CASES

Case No., sex and age (yrs.)	Date	BMR	*Serum*								*Urine*	*Treatment*		*Diagnosis*
			SPI	Albumin	Globulin	Cholesterol		Fatty acid		Lipid P	Ketosteroids	Thyroid substance	Methyl testosterone	
						Total	Free	Total	Neutral Fat					
		%	γ %	Gm. %	Gm. %	mg. %	mg. %	mM/L	mM/L	mg. %	mg./day	Gm./day	mg./day	
1. (B91214)	1947													
F 31	12/ 3		2.9	4.0	3.5									Craniopharyngioma
	12/11			2.9	3.2									
	12/16		5.3	3.3	3.9	105	65	16.4	8.9	11.0				
	1948													
	2/20		4.8			229	62	15.9	7.0	10.3				
2. (B76181)	1946													
M 26	1/26	−28	3.4											Craniopharyngioma
	3/21		2.9			229		10.9			1.7			
	1947													
	1/13		3.2			146		7.9				0.18		
	8/ 4		3.9								3.9	0.24	20	
	8/21			3.6	2.8							0.24		
	10/13		1.3									0.24		
	12/15	−32	3.3									0.36	30	
	1948													
	2/16	−27	4.0			194	53	10.5	3.3	8.9		0.36	30	
	5/17	−27	4.3									0.36	30	
	8/16	−23	3.8									0.36	30	
	11/15	−30	2.7									0.36	30	
	1949													
	2/14		2.6			203	61	13.3	4.3	9.4		0.36	30	
3. (PO (BB))	1948													Chromophobe adenoma
M 66	10/22		3.9	3.0	3.0	183	57	11.0	4.9	6.5	2.5	0.12		
4. (B70982)	1947													Chromophobe adenoma
F 30	7/23	−18	3.5			227		11.3						
5. (71570)	1947													Craniopharyngioma
M 60	7/15			2.1	2.9									
	7/21		2.6			108	25	6.4	1.2	6.3				
	8/19			2.1	2.8								20	
	8/29		1.8	1.2	3.1								30	
	9/ 9		2.0	1.8	3.4							0.03	30	
6. (B74923)	1946													Chromophobe adenoma
M 28	2/ 7		3.3								4.4			
	3/12	−31									3.4			
	3/27		3.6	4.5	2.2	206	66	29.8	20.2	12.0				
	5/ 3		6.7									0.06		
	6/ 7	−22										0.06		
	1947													
	1/11	−17										0.12		
	5/10										3.0	0.06		
	8/ 6	−29	1.7									0.06		

TABLE 1—(*continued*)

Case No., sex and age (yrs.)	Date	BMR	*Serum*								*Urine*	*Treatment*		*Diagnosis*
			SPI	Albumin	Globulin	Cholesterol		Fatty acid		Lipid P	Ketosteroids	Thyroid substance	Methyl testosterone	
						Total	Free	Total	Neutral Fat					
		%	γ %	Gm. %	Gm. %	mg. %	mg. %	mM/L	mM/L	mg. %	mg./day	Gm./day	mg./day	
7. (B69216) M 44	1945													Suprasellar tumor
	5/25	−29	1.7			247		12.3		9.3				
	6/18	−33	4.7									0.06		
	1946													
	5/ 6		2.7			250		11.3				0.06		
	11/22		2.2									0.06		
	1947													
	10/24		3.3	3.6	3.1	201		11.5				0.06		
	1948													
	11/ 5		4.5			243	75	13.6	5.2	9.1		0.09		
8. (99362) M 47	1947													Chromophobe adenoma
	9/19	−16	2.9											
	10/14		5.1	3.8	2.5	281	80	16.4	5.8	11.7	4.0			
	1948													
	1/ 9		2.5									0.03	30	
	10/14		2.3	3.8	3.4	189		10.5				0.03	30	
	11/15	+ 3	1.6	3.5	3.5	178	59	9.1	2.9	6.9		0.03	30	
	11/16		1.2	3.6	3.5	185	56	10.1	3.3	7.6		0.03	30	
	11/17	− 3	1.8	3.5	3.1	172	55	15.7	10.0	6.2		0.12	30	
	11/18		1.7			165	48	10.0	4.3	6.2		0.12	30	
	11/19		2.1	3.3	3.2	150	48	8.7	3.4	5.9		0.12	30	
9. (A79550) M 18	1938													Chromophobe adenoma
	7/26	−17		6.1	2.2	201		14.9						
	1946													
	3/20		4.4								10.2			
	1948													
	10/12		5.7			276	87	18.5	8.7	10.8				
	10/19		5.5	2.4	3.0									
	1949													
	3/17		4.5			274	70	16.1	5.2	10.0				
10. (C20693) F 57	1949													Chromophobe adenoma
	1/ 6		3.2	3.6	3.1	357	117	14.5	6.8	3.2				
	3/ 1		3.6	3.9	3.1	300	93	16.4	3.6	18.0		0.12		
	3/11					258	81	20.0	8.9	13.5				
11. (C21235) F 32	1949													? Acromegaly
	1/20		2.5	4.8	3.0	173	28	12.1	3.7	8.9				
12. (C21335) F 42	1949													Chromophobe adenoma
	1/24			4.1	3.6	308	80	18.8	6.9	13.1				

TABLE 1—(*continued*)

Case No., sex and age (yrs.)	Date	BMR	*Serum*								*Urine*	*Treatment*		*Diagnosis*
			SPI	Albumin	Globulin	Cholesterol		Fatty acid		Lipid P	Ketosteroids	Thyroid substance	Methyl testosterone	
						Total	Free	Total	Neutral Fat					
		%	γ %	Gm. %	Gm. %	mg. %	mg. %	mM/L	mM/L	mg. %	mg./day	Gm./day	mg./day	
13. (C22269) F 19	1949 2/21			4.2	3.2	159	34	10.3	3.8	7.2				Chondroma
14. (B6180) M 23	1947 1/13	−23	5.0	3.9	3.1	188		13.2						Chromophobe adenoma
	1/20										18.0			
	1/22										27.0			
15. (B99513) F 50	1947 7/16	− 4												Adenoma from pars intermedia
	11/10		2.7	3.4	2.9									
16. (A99433) F 24	1940 1/11	− 7				190	49	11.4						Chromophobe adenoma
	1949 4/ 4		5.0			191	51	13.0	8.9	5.2				
17. (A52397) F 69	1945 9/27	+23	6.1											Eosinophilic adenoma
	10/ 2	+15												
	1946 8/ 1	+11	6.6	4.0	1.7						6.2			
	1948 10/11	−22	6.4	3.2	2.7									
18. (B96690) F 12	1947 11/ 7		2.3											Craniopharyngioma
	1948 5/20		3.8			256		15.3				0.03		
19. (PO (AA)) F 26	1948 3/ 5		3.7											Diabetes insipidus
	4/27		5.7									0.03		
	7/ 2		5.7									0.06		
	1949 1/21		4.7									0		
20. (PO (HE)) F 16	1946 3/ 9	−15	3.0			195		11.9						Infantilism, cause unknown
	4/26	+11	4.1									0.06		
	1947 7/ 7	+ 7	2.9									0.12		
	10/13		5.0									0.12	20	
	1948 2/24		1.5			140						0.12		

of Hald, utilizing either conventional chemical procedures (8) or the flame photometer (9), bicarbonate by the technique of Van Slyke and Neill (10), chloride by Hald's modification of the micro procedure of Patterson (11), and blood glucose by the method of Benedict (12) with Rothberg and Evans tubes (13). Through 1946 the serum proteins were fractionated with sodium sulfate according to the technique of Howe (14); after that, Milne's (15) modification of Howe's technique following the principle of Majoor (16) was employed. The actual measurement of nitrogen was carried out by a macro-Kjeldahl procedure. Copper sulfate was used as catalyst, with superoxol to accelerate oxidation, until January 21, 1946; after that mercury was substituted as catalyst.

RESULTS

Brief protocols giving essential data about the patients will be found at the end of the paper. The chief laboratory data are given in Tables 1 and 2.

In all but 5 of the 18 patients in whom SPI was measured, the initial value was less than 3.8γ per cent, the lowest limit of the normal range, and in 1 of these 5, B. B., it was only 3.9γ per cent. In most of them it was far below this, at concentrations that would, under ordinary conditions, justify a diagnosis of myxedema. Nevertheless, none of these patients had signs or symptoms indicative of hypothyroidism. The basal metabolism of most of those in which it was determined was depressed to hypothyroid levels. On the other hand, only in Cases 10 and 12 was cholesterol greater than 300 mg. per cent. In 4 cases, Nos. 1, 2, 5 and 20 (Table 1), it was at some time distinctly low. In 2 subjects, Cases 9 and 14, basal metabolism was depressed to hypothyroid levels without either reduction of SPI or elevation of cholesterol. The low value for cholesterol in Case 1 can be attributed to the effects of the recent operation. It will be noted that at the time of this observation serum albumin was also somewhat reduced. The hypolipemia, like the hypoalbuminemia in Case 5 may be ascribed to the cachectic condition of the patient (17). In no other case was serum albumin low enough to account for the low SPI's (1). The SPI in Case 1 after the first observation, rose to normal; but at the times of the last two determinations this patient's condition was complicated by a recent craniotomy and by the onset of her terminal episode, respectively. The SPI in Case 8 on one occasion rose to 5.1γ per cent without evident cause. In no other instances did SPI rise spontaneously from its hypothyroid concentration. It was not possible, for various reasons, to test the response of all patients to the administration of thyroid substance. In Case 1 the terminal illness started before the effect of thyroid could be ascertained. The deterioration

can not be attributed to the thyroid because it had begun before the latter was given. In Cases 6, 7 and 8 the men complained of palpitation and nervousness when they were given doses of 0.12 Gm. per day. Unfortunately, no measurements of SPI were made on these occasions because the patients reduced the doses without reporting. In Case 6, after the ingestion of 0.12 Gm. daily for a month, there were no objective signs of hyperthyroidism and the basal metabolism was −17 per cent. In Case 8, 0.12 Gm. of thyroid was given daily for three days without subjective or objective effect. No serious efforts were made to increase the doses in Cases 7 and 8 because of the evidences of adrenocortical insufficiency. In Case 5 the patient was treated most conservatively because of his cachectic state and behavior difficulties. In this case also it was felt that the low SPI might be referable to the hypoalbuminemia rather than to hypopituitarism. Some of the patients have not been observed long enough to ascertain their reactions to thyroid. When the effects of thyroid therapy were followed closely, SPI seemed to be not altogether unresponsive. It usually rose to the lower limits of the normal range, but these rises were not sustained. The most striking example of this is Case 2; the SPI rose to about 4γ per cent during the administration of 0.24 Gm. of thyroid daily and again with 0.36 Gm. but each time relapsed to hypothyroid concentrations again. The basal metabolism in this case remained consistently low, between −23 and −32 per cent, but serum cholesterol never rose above normal.

Other endocrine functions were variably affected. In Case 1 gonadal activity appeared to be impaired, but not abrogated. In Cases 2, 3, 6, 7 and 8 there was striking hypogonadism, evident in general physical characteristics and in urinary ketosteroid excretion. In Case 5 less certainty can be expressed about the patient, who was distinguished by his cachexia and anorexia. In Case 18 there was also extreme anorexia with arrested development. In Case 16, there was not only precocious amenorrhea, but associated menopausal symptoms.

Adrenocortical insufficiency was demonstrated in only 2 patients in the series, Cases 7 and 8 (Table 2). Both appear to have had acute Addisonian crises before they came under observation. Both went into collapse and developed hyponatronemia when they were deprived of salt. A short attempt at maintenance with methyl testosterone was unsuccessful in Case 8. Both patients responded to implants of desoxycorticosterone acetate (DOCA). In spite of the fact that they wasted salt, neither developed hypoglycemia within five hours after the intravenous injection of 25 Gm. of glucose while in the postabsorptive state, nor was spontaneous hyperglycemia ever discovered.

TABLE 2. ELECTROLYTES AND BLOOD SUGAR

Case No., sex and age, (yrs.)	Date	*Blood glucose*		*Serum*				*Diagnosis and remarks*
		Fasting	After 5 hrs.[1]	HCO_3	Cl	Na	K	
		mg. %	mg. %	mEq./L	mEq./L	mEq./L	mEq./L	
1. (B91214)	1947							Craniopharyngioma
F 31	12/ 3	79	82	25.1	101.3	145.0		
	12/ 6			27.6	95.7	141.3		After salt restriction[2]
	12/ 8	80				136.5		Morning of operation
	12/11			21.2	98.1	138.0		
	12/16			29.1	99.9	140.6		
	12/18	63	71			138.3		After salt restriction
	1948							
	4/ 2	99		26.4	94.3	141.9	3.9	
	4/ 4					171.5	4.4	3 P.M. day after operation
					124.3	164.4	3.7	6 P.M. after pituitrin and glucose
	4/ 5			26.5	115.6	153.7	2.6	Infusion of glucose and KCl
	4/ 6				106.1	147.0	3.7	
	4/ 7				113.6	151.7	3.8	
	4/ 8				94.9	140.0	3.6	
	4/ 9				100.4	144.6	3.3	
	4/13			28.3	113.6	162.9	5.0	
	4/14			26.2	113.2	161.9	3.8	
2. (B76181)	1946							Craniopharyngioma
M 26	1/23			24.8	101.0			
	1/31			21.2	101.5			After salt restriction
	1947							
	8/21			24.6	104.7			
	1949							
	2/15	63	55	24.3	100.0	143.2		
	2/19			28.8	101.8	139.3	4.2	After salt restriction
3. (PO (BB))	1948							Chromophobe adenoma
M 66	10/22			29.2	102.2	144.0		
5. (71570)	1947							Craniopharyngioma
M 60	7/18			19.2	107.0	138.0		
	7/28	63		21.5	104.6			
	7/31			20.1	99.0			After salt restriction
	9/ 9			17.3	97.5	136.7		
	9/26			17.6	102.4			After serum albumin injections
6. (B74923)	1946							Chromophobe adenoma
M 28	2/ 7	85	84					
	3/12	79	72	26.4	103.3			
	3/26	61	68	26.5	101.0			
	4/ 1			26.4	98.4			After salt restriction
	5/ 3			23.6	101.9			
	6/ 7			25.2	101.6			
	1947							
	5/10			27.3	101.6			
7. (B69216)	1945							Suprasellar tumor
M 44	5/25	74	(63)[2]					
	6/ 1			25.5	84.4			After salt-poor diet
	6/ 4			26.3	84.3			After salt-poor diet
	6/ 5			23.7	91.9			After infusion of NaCl
	6/ 6			23.2	90.2			On NaCl 10 Gm. DOCA 5 mg.
	6/12			24.2	93.1			On NaCl 10 Gm. DOCA 5 mg.
	6/27			25.4	95.6			On NaCl 10 Gm. DOCA 7 mg.
	7/ 2			26.2	98.9			DOCA implants June 29
	9/28			26.8	98.8			
	1946							
	1/25			27.0	93.1			
	5/ 2	76		25.5	97.7			DOCA implants renewed
	11/22			26.7	102.1			
	1947							
	10/24			30.2	100.1			DOCA implants renewed Nov. 5
	1948							
	2/27			27.1	103.1			
	10/29	76		26.6	103.4			DOCA implants renewed Nov. 5
8. (99362)	1947							Chromophobe adenoma
M 47	10/14	93	(76)[2]	23.8	102.4	138.0	5.1	
	10/17					120.0	5.1	6 P.M. Salt restriction Oct. 15
		81			86.2	118.9	4.9	9 P.M. Infusion NaCl and glucose
	10/18			20.5	95.0	127.2	4.4	After infusion of 2500 cc. with NaCl 33.5 Gm., glucose 75 Gm.

[1] Five hours after the intravenous injection of 50 cc. of 50 per cent glucose solution.
[2] Two hours after the intravenous injection of 50 cc. of 50 per cent glucose solution.
[3] To avoid serious reactions, the degree and duration of salt restriction were varied from case to case. In most instances, when no symptoms of adrenocortical insufficiency had been noted, the patients were given at once a diet prepared without addition of salt and containing 2 to 3 Gm. of NaCl. Urine and serum were analyzed at one or two day intervals. Intermediate analyses have been omitted in most instances for the sake of brevity.

TABLE 2—(*continued*)

Case No., sex and age (yrs.)	Date	*Blood glucose*			*Serum*			*Diagnosis and remarks*
		Fasting	After 5 hrs.[1]	HCO_3	Cl	Na	K	
		mg. %	mg. %	mEq./L	mEq./L	mEq./L	mEq./L	
	10/20			25.5	95.3			On regular diet
	10/21	76	70			122.8	4.4	
	10/24			25.6	79.0	131.8		NaCl 5 Gm. added to diet
	10/25					133.8		NaCl 9 Gm. added to diet through 11/2
	10/27			27.2	96.1	133.8		DOCA implants
	10/29			27.5	95.2			
	10/30			26.8	90.3	135.8	5.1	
	11/14			22.7	97.6	132.2	4.7	
	11/28			26.1	96.2	133.2	4.8	
	12/12	77		26.0	98.7	136.0	4.5	
	1948							
	1/ 9			24.8	99.5	140.0	5.1	
	6/18			28.5	97.6	143.9	4.4	
	10/14			27.8	97.2			
	11/16			25.8	93.3	133.7		DOCA implants renewed 11/20
9. (A79550)	1938							Chromophobe adenoma
M 18	7/26	75	(78)[2]					
	1945							
	3/20			27.0	99.7			
	1947							
	8/15	126		23.9	90.7			
	1948							
	10/12	94						
	10/13			30.1	104.1	139.5	4.0	
	10/15			27.2	95.4	135.1	3.5	
	10/18			27.2	94.9	131.2		
	1949							
	3/17			28.4	95.9	141.5	3.9	
10. (C20693)	1949							Chromophobe adenoma
F 57	1/ 5	83	79	27.3	91.5	137.0	4.0	
	1/10			26.5	92.5	131.3		After salt restriction
	1/14			28.3	88.4	128.9		After further salt restriction
	1/20			25.6	91.1	136.0		
	3/ 1	88		26.6	96.5	145.9	4.6	
	3/ 3			22.0	97.0	136.4	3.8	After salt restriction
	3/10			27.6	91.6	136.8	4.9	After operation
11. (C21235)	1949							?Acromegaly
F 32	1/18	69	61	26.4	97.5	137.5	4.0	
12. (C21335)	1949							Chromophobe adenoma
F 42	1/19	81			102.8			
	1/21	74	80	26.6	96.6	134.0	4.1	
	1/28			27.9	97.7	143.8	4.7	
13. (C22269)	1949							Suprasellar cyst
F 19	2/19	89	80	28.7	93.5	137.8	4.2	
	2/25			27.7	95.5	140.5		After salt restriction
	3/ 1			24.4	94.3	144.3		
14. (B6180)	1947							
M 23	1/15	85	89					Chromophobe adenoma
16. (A99433)	1940							Chromophobe adenoma
F 24	1/10	90	(71)[2]					
17. (A52397)	1946							Eosinophilic adenoma
F 70	7/30	172		25.4	97.1			
	1948							
	10/ 6	208		26.8	104.2	138.0		

DISCUSSION

The most striking feature of the whole series is the frequency of reductions of SPI without the usual symptoms and signs of hypothyroidism. Basal metabolism was, it is true, low in those cases in which it was determined, but the clinical features of hypothyroidism were lacking and serum cholesterol was seldom elevated. Only in Case 5 was there sufficient hypoalbuminemia to account for the low SPI. The natural reaction is to attrib-

ute these low iodines to hypothyroidism secondary to deficiency of the thyrotropic hormone of the pituitary. The low basal metabolisms seem to support this hypothesis. It seems odd, however, that thyrotropic activity should be injured so much more frequently than other anterior pituitary functions. Furthermore, in some instances low SPI is associated with intracranial disorders in which there is no other reason to suspect anterior pituitary deficiency. In Case 11, for example, acromegaly was suspected. Although the most prominent feature in Case 18 was diabetes insipidus, the patient's growth and development were retarded and the possibility is not excluded that the craniopharyngioma may have impinged upon the anterior lobe of the pituitary. There is no reason, however, to suspect this in Case 19, which was one of simple diabetes insipidus, presumably of embolic origin.

Although basal metabolism, when determined, proved to be low, cholesterol and other lipid fractions were not usually elevated as they are in hypothyroidism. There is no convincing reason to believe that in this respect the hypothyroidism of pituitary deficiency should differ from primary hypothyroidism, unless it is accompanied by malnutrition. Thompson and Long (18) found that in dogs the hypercholesterolemia that followed thyroidectomy was abolished by removal of the hypophysis. When Entenman, Chaikoff and Reichert (19) repeated these experiments with pair-fed animals they found that the hypocholesterolemia that followed removal of the pituitary arose only from failure of the hypophysectomized animals to eat. The cholesterol of simply thyroidectomized animals rose no more than that of animals which had also been hypophysectomized, if the diets of the former were limited to the quantities of food taken by the latter. It has already been pointed out that the serum cholesterol of patients with myxedema may be reduced by malnutrition (17, 20, 21). This has been further substantiated by additional unpublished studies. In the present series, the patients in Cases 7 and 8 were distinctly but not pathologically thin, whereas in Cases 1, 2, 10, 11 and 19 they were distinctly obese, and in Case 20, plump, though underdeveloped. Only in Cases 5 and 18 did the picture suggest pituitary cachexia. In Case 5 this condition was accompanied by extreme hypoalbuminemia.

The patterns of the serum lipids in patients with disorders of the pituitary gland have received little attention. One feature of the lipids in the present series deserves passing mention. The serum of normal persons in the postabsorptive state contains little neutral fat; the fatty acids of the serum belong chiefly to cholesterol esters and phospholipids. In a large series of analyses of the serum from patients with a variety of disorders and diseases, as yet unpublished, neutral fat-fatty acids seldom exceeded 6 mM per liter, regardless of the concentration of total fatty acids, unless

there was disease of the liver, nephritic hyperlipemia or diabetes. High neutral fat was not encountered in uncomplicated hypothyroidism (21). In the present series, however, in the absence of any of the disorders that usually raise neutral fat, neutral fat-fatty acids exceeded 6 mM per liter on several occasions. No great significance can be attached to the irregular incidence of this disturbance except that it does distinguish the lipid patterns of these patients in an additional respect from those of patients with primary hypothyroidism. Ratios of free to total cholesterol, on the other hand, were normal with one exception, namely, the second observation in Case 1, when a high cholesterol ratio appeared during recovery from a craniotomy.

Although the SPI and basal metabolism of some of the patients rose after the administration of thyroid or other changes of therapy, these rises were usually temporary. Only in Case 19 has the increase of SPI been sustained. Variations of serum cholesterol were inconsistent. It is characteristic of the patient with myxedema to react promptly and quantitatively to active thyroid substance (22), the reaction being reflected in SPI, basal metabolism and serum cholesterol. On the other hand, many euthyroid subjects are able to tolerate large doses of thyroid without chemical or clinical evidences, or with only transitory evidences of hyperthyroidism (23). The presence of a normally functioning thyroid gland appears to enable persons to dispose of superfluous quantities of thyroid hormone. If such normal subjects are given iodine the element is rapidly picked up by the thyroid gland, where part of it is incorporated in thyroglobulin in the form of thyroxine. Subsequently the iodine is eliminated without producing hyperthyroidism. It has been presumed that the patient with secondary hypothyroidism due to lack of thyrotropic hormone should respond like the primary hypothyroid subject to thyroid substance. The presence of a potentially active thyroid gland may enable patients with deficient thyrotropic activity to dispose of thyroid substance as normal subjects do. The thyrotropic hormone not only stimulates the thyroid gland to hyperplasia, but also to elaboration of hormone and its release into the circulation. The absence of thyrotropic hormone may lead to the imprisonment and destruction of thyroxine.

The absence of other signs or symptoms of deficient thyroid activity seems incompatible with either primary or secondary hypothyroidism. With the exception of extreme hypoalbuminemia in Case 5, however, none of the other factors that have been found to lower SPI is apparent in these cases. Disturbances of the function of other endocrine glands besides the thyroid are so inconsistent that the low SPI's can not be attributed to these collateral disturbances. The hypothesis that the serum iodine deficiency is determined by injury to adjacent portions of the brain, especially

the hypothalamus, although it can not be excluded, requires more inquiry and examination of patients with other types of intracranial injury. In this series, the only subject who displayed symptoms strongly indicative of hypothalamic injury, Case 17, had a normal SPI on two occasions, though her basal metabolism was low. The autopsy in Case 1 throws some light on the subject. There can be no doubt that the thyroid, breasts and ovaries of this patient were hypoplastic. Presumably their functional activity was greatly depressed, but not abolished. Although her SPI was initially extremely low, it did rise under stimulation to low normal levels. The absence of characteristic symptoms and signs of hypothyroidism may denote that thyroid hormone was delivered at a continuing low rate to the tissues. It is notorious that myxedema and the other most obvious signs of thyroid deficiency are abolished by doses of thyroid too small to restore the euthyroid state. The variability of SPI and its reactions in the other cases may depend upon the degree of thyrotropic deficiency. The high serum cholesterols in Cases 10 and 12 may indicate that these patients have a high degree of insufficiency. There has not yet been time to ascertain their reactions to treatment with thyroid.

Adrenocortical function appears to be less often impaired than any of the other endocrine functions controlled by trophic hormones of the anterior pituitary. It may be that the tests employed for its assessment were not sufficiently sensitive. The salt restriction test did detect adrenocortical insufficiency in the 2 patients in which it seems to have been important. None of the group developed hypoglycemia within five hours after the administration of glucose. That there may be dissociation of the trophic functions in hypopituitarism is clear from Case 1; at autopsy there were normal adrenal glands despite the atrophy of thyroid, breasts and ovaries.

It has been reported that it may be dangerous to treat hypopituitary patients with thyroid (24, 25); indeed, fatalities have been reported as a result of this procedure. In this series it appears to have had no ill effects. In fact, it had no demonstrable effects. Only moderate doses, to be sure, were given to most of the cases. A larger dose might have had a malignant effect upon the patient in Case 5, who had a cachectic syndrome. It does not, however, seem to have done any harm to the patient in Case 18, who had anorexia and retarded growth and development. It is hard to understand how it could be injurious if it does not alter SPI or metabolism. The 2 patients with adrenal insufficiency may have been protected by desoxycorticosterone and other supportive measures. The use of thyroid may be challenged on the grounds that it is a futile measure; but, if its effects are carefully controlled, it is apparently a safe procedure.

If the dissociation of trophic functions in the majority of these patients is bewildering, the complete absence of trophic disorders in Case 9 is

baffling. The tumor, which was identified as a chromophobe adenoma, was removed four times and the operative notes describe it as arising from the sella turcica. Nevertheless, the gonadal and adrenocortical functions have not been demonstrably impaired and SPI remains within normal limits.

SUMMARY

The endocrine functions of 20 patients, 19 of whom actually or presumably had tumors or other lesions in or adjacent to the pituitary gland, have been assessed. The concentration of precipitable iodine in the serum, SPI, was frequently reduced to levels characteristic of hypothyroidism, whereas the functions of the gonads and the adrenal cortices were less frequently affected. Basal metabolism, when it was measured, was usually also low, but serum cholesterol was usually within normal limits and clinical symptoms and signs of hypothyroidism were lacking. SPI did not respond or responded only transiently to administration of thyroid substance. The significance of the deficiency of serum iodine is discussed.

REFERENCES

1. Peters, J. P., and Man, E. B.: The relation of albumin to precipitable iodine of serum, *J. Clin. Investigation* **27**: 397, 1948.
2. Man, E. B.; Smirnow, A. E.; Gildea, E. F., and Peters, J. P.: Serum iodine fractions in hyperthyroidism, *J. Clin. Investigation* **21**: 773, 1942.
3. Man, E. B., and Gildea, E. F.; A modification of the Stoddard and Drury titrimetric method for the determination of the fatty acids in blood serum, *J. Biol. Chem.* **99**: 43, 1932.
4. Man, E. B., and Gildea, E. F.: Notes on the extraction and saponification of lipids from blood and blood serum, *J. Biol. Chem.* **122**: 77, 1937.
5. Man, E. B., and Peters, J. P.: Gravimetric determination of serum cholesterol adapted to the Man and Gildea fatty acid method, with a note on the estimation of lipoid phosphorous, *J. Biol. Chem.* **101**: 685, 1933.
6. Man, E. B.: A note on the stability and quantitative determination of phosphatides, *J. Biol. Chem.* **117**: 183, 1937.
7. Bogdanovitch, S. B., and Man, E. B.: The effects of castration, theelin, testosterone and antuitrin-S on the lipoids of blood, liver and muscle of guinea pigs, *Am. J. Physiol.* **122**: 73, 1938.
8. Hald, P. M.: Notes on the determination and distribution of sodium and potassium in cells and serum of normal human blood, *J. Biol. Chem.* **163**: 429, 1946.
9. Hald, P. M.: The flame photometer for the measurement of sodium and potassium in biological materials, *J. Biol. Chem.* **167**: 499, 1947.
10. Van Slyke, D. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. *J. Biol. Chem.* **61**: 523, 1924.
11. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. II. Methods. Baltimore, Williams and Wilkins, 1932, p. 838.
12. Benedict, S. R.: The estimation of sugar in blood and normal urine, *J. Biol. Chem.* **68**: 759, 1926.

13. ROTHBERG, V. E., and EVANS, F. A.: Studies with the Folin and Wu blood sugar method, *J. Biol. Chem.* **58**: 435, 1923. A modified Folin and Wu blood sugar method, Ibid. 443.
14. HOWE, P. E.: The determination of proteins in blood—a micro method, *J. Biol. Chem.* **49**: 109, 1921.
15. MILNE, J.: Serum protein fractionation: a comparison of sodium sulfate precipitation and electrophoresis, *J. Biol. Chem.* **169**: 595, 1947.
16. MAJOOR, C. L. H.: The possibility of detecting individual proteins in blood serum by differentiation of solubility curves in concentrated sodium sulfate solutions. II. Comparison of solubility curves with results of electrophoresis experiments, *J. Biol. Chem.* **169**: 583, 1947.
17. MAN, E. B., and GILDEA, E. F.: Serum lipids in malnutrition, *J. Clin. Investigation* **15**: 203, 1936.
18. THOMPSON, K. W., and LONG, C. N. H.: The effect of hypophysectomy upon hypercholesterolemia of dogs, *Endocrinology* **28**: 715, 1941.
19. ENTENMAN, C.; CHAIKOFF, I. L., and REICHERT, F. L.: Blood lipids of the hypophysectomized-thyroidectomized dog, *Endocrinology* **30**: 802, 1942.
20. MAN, E. B.; GILDEA, E. F., and PETERS, J. P.: Serum lipoids and proteins in hyperthyroidism, *J. Clin. Investigation* **19**: 43, 1940.
21. PETERS, J. P., and MAN, E. B.: The interrelations of serum lipids in patients with thyroid disease, *J. Clin. Investigation* **22**: 715, 1943.
22. WINKLER, A. W.; CRISCUOLO, J., and LAVIETES, P. H.: Quantitative relationship between basal metabolic rate and thyroid dosage in patients with true myxedema, *J. Clin. Investigation* **22**: 531, 1943.
23. WINKLER, A. W.; LAVIETES, P. H.; ROBBINS, C. L., and MAN, E. B.: Tolerance to oral thyroid and reaction to intravenous thyroxine in subjects without myxedema, *J. Clin. Investigation* **22**: 535, 1943.
24. BULGER, H. A., and BARR, D. P.: Metabolic studies of pituitary insufficiency, *Endocrinology* **20**: 137, 1936.
25. MEANS, J. H.: The Thyroid and Its Diseases, ed. 2. Philadelphia, J. B. Lippincott Co., 1948.
26. ELKINTON, J. R., and TAFFEL, M.: Prolonged water deprivation in the dog, *J. Clin. Investigation* **21**: 787, 1942.
27. WINKLER, A. W.; DANOWSKI, T. S.; ELKINTON, J. R., and PETERS, J. P.: Electrolyte and fluid studies during water deprivation and starvation in human subjects, and effect of ingestion of fish, of carbohydrate, and of salt solutions, *J. Clin. Investigation* **23**: 807, 1944.

CASE REPORTS

Case 1 (*B91214*) *M. B.*, female, born in 1916, noticed blurring of vision in 1942. In 1946 this increased, accompanied by occipital headaches. Her menses became irregular in 1945. When admitted to the hospital December 16, 1946, she was well developed, slightly overweight and, except for her eyes, seemed quite healthy. The optic discs were pale, and the vision in both eyes reduced to 20/200. There was a bitemporal hemianopsia with restriction of the remainder of the visual fields as well. X-ray examination of the skull revealed expansion and erosion of the sella turcica together with a soft tissue mass above the posterior margin of the hard palate. A month later she was readmitted to the hospital for x-ray treatment. In the meantime her vision had deteriorated further and her menses had ceased. December 2, 1947, she entered the hospital for the third time be-

cause of continued deterioration of vision and further destruction of the sella turcica. In spite of amenorrhea, secondary sex characteristics and libido had not apparently changed. A craniotomy was performed and as much as possible of the craniopharyngioma was removed on December 8. Prolonged blood sugar tolerance curves and salt withdrawal tests both before and after operation gave normal results. Although her eyes did not improve, she had no other symptoms after operation except an insatiable appetite. March 19, 1948, 0.03 Gm. of thyroid daily was prescribed because she was gaining weight. Shortly before this some changes of behavior had been noted, together with

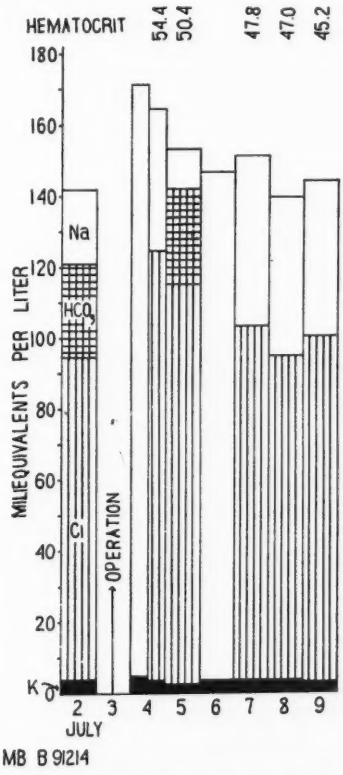


FIG. 1. Serum electrolytes in Case 1 after operation. The left hand column represents, for comparison, the average concentrations of electrolytes in the serum of normal adults. The concentration of sodium + potassium is represented by the total height of each column, upon which the concentrations of bicarbonate and chloride are superimposed.

somnolence and extreme exhaustion. March 26 she was seized with a severe headache, dizziness, nausea and vomiting. March 31 she became confused and unable to eat or sleep. April 2 she was admitted to the hospital, pale, extremely weak, confused, and somnolent, with slow hesitating speech. The bone flap was bulging. Craniotomy was

immediately performed and a cyst, which had penetrated the third ventricle, was extirpated as far as possible. Her condition after operation seemed good, but on the following morning she became increasingly drowsy and confused and appeared dehydrated. It was then discovered that, with an intake of only 3400 cc. in the preceding twenty-four hours and despite some elevation of the temperature and the operative procedure, she had excreted 4300 cc. of urine. The specific gravity of a urine specimen obtained on the morning of April 4 proved to be only 1.005 although the urine gave a 3+ reaction for sugar (presumably the result of an infusion of glucose solution). Examination of her blood revealed striking hemoconcentration (a relative blood cell volume of 54.4 per cent) and an extraordinarily high concentration of sodium in the serum. The course of her serum electrolytes is illustrated in Figure 1. It was evident that she had developed an acute diabetes insipidus. Being unable to take fluids of her own volition had resulted in extreme dehydration with the characteristic reaction on the part of the kidneys that has been described by Elkinton, Taffel, Winkler, *et al.* (26, 27); accelerated reabsorption of sodium chloride causing the concentrations of these ions in the serum to rise. Such a reaction has been predicted in diabetes insipidus, but has not been demonstrated in man because restriction of water to the degree required to elicit the reaction is intolerable. By administration of larger amounts of fluid and injections of pituitrin at frequent intervals the diuresis was partly controlled. Hemoconcentration and dehydration were greatly mitigated and the concentrations of sodium and chloride in the serum were brought down almost to normal. Unfortunately no record of urine volumes could be obtained because the patient was incontinent. She succumbed to an infection of the ventricles on April 15.

At autopsy it was found that the tumor extended backward as far as the interpeduncular space. The pituitary was greatly reduced in size and appeared to contain predominantly basophilic elements, although groups of eosinophilic cells were also visible. The thyroid gland was extremely small, weighing only about 4 grams and, microscopically showed minute follicles lined by flattened cells. The breasts, though full and rounded in appearance, contained only small islands of hypoplastic glandular tissue, consisting almost entirely of fat and connective tissue. The ovaries were small and contained many unripe, but no developing follicles nor corpora lutea. The uterus was also hypoplastic and the mucosa and glands, though not truly atrophic, appeared relatively inactive. The adrenals in size and in gross and microscopic appearance were essentially normal. The thymus consisted chiefly of fat and was not extraordinary for a person of this age. Only one parathyroid gland was found and it was of normal size. The pancreas was normal.

Case 2 (*B76181*) *S. B.*, male, born in 1920, about the middle of 1944 developed a conjunctival hemorrhage in his left eye. Shortly after this the eye deviated outward and he noticed blurred vision and diplopia. He was extremely small for his age, being only 4 feet 11 inches in height and weighed 119 pounds. His genitalia were infantile and he lacked both pubic hair and beard. The optic nerve heads were white, he had a right hemianopsia and the left visual field was extremely restricted. X-ray examination revealed a bone age of only 13 and an enlarged sella turcica. Craniotomy was performed on January 28, 1945, and a craniopharyngioma in the region of the right optic nerve was removed. His laboratory findings and subsequent course are outlined in Table 1. His general condition has remained remarkably good. The disorders related to the tumor have progressed only slightly. Development has not advanced.

Case 3 (*B. B.*) male, born in 1883, began in 1939 to suffer from headaches in the right temporal region. This was associated with gradual loss of axillary and body hair, loss of

potency, weakness, pallor and intolerance to cold. Because of a basal metabolism of −15 per cent, 0.06 Gm. of thyroid daily was prescribed. In 1942, because of enlargement of the sella turcica and some restriction of his visual fields, he was given x-ray therapy, which relieved the headaches, but had no other effects. In June of 1948 he was given another course of x-ray treatment because his headaches had recurred and his visual fields had become further restricted. Again the headaches alone were improved. At this time the dose of thyroid was increased to 0.12 Gm. daily. When seen on July 23 he had obvious signs of hypogonadism, an eczematous condition over the right extrenal malleolus and a moderate secondary anemia. He had no signs suggestive of thyroid deficiency. It was impossible to test his reaction to restriction of salt because he came from out of town and did not wish to enter the hospital. Serum sodium, however, was 144, chloride 102.2, and bicarbonate 29.2 mEq. per liter. There was no story suggestive of either hypoglycemia or sodium deficiency.

Case 4 (*B70982*) *M. K.*, female, was born in 1917. Shortly after an attack of bacillary dysentery in 1930, she ceased to menstruate, although secondary sex characteristics and libido did not change. Because her basal metabolism proved to be −36 per cent, she was given thyroid, which she continued to take thereafter in doses of 0.12 to 0.18 Gm. daily. Between that time and 1945 she gained 25 pounds in weight, but noted no change of disposition nor of the texture of skin or hair. She was married in 1942, but did not become pregnant. She had an appendectomy in 1943. In 1944 a course of gonadotropin had no noticeable effect. When seen in July, 1945, her physical examination was essentially normal. X-ray examination revealed asymmetrical expansion of the sella turcica.

Case 5 (*71570*) *W. S.*, male, born in 1887, is a physician. In October of 1942, during removal of an upper first molar tooth the antrum was entered. The sinus failed to close. In 1943, a roentgenogram taken to ascertain whether there was a foreign body in the anthrum, revealed enlargement of the sella turcica. In August, 1944, he fainted and remained unconscious for four days. At this time the question arose whether there had been a hemorrhage into the tumor. In August, 1946, he again fainted and fell down the stairs, but suffered only abrasions. From the beginning of his illness in 1942 he lost weight steadily. This process became accelerated after the episode of unconsciousness in 1944. From this time on, appetite and vigor decreased steadily. When admitted to the hospital June 30, 1947, he was almost emaciated. Pubic and axillary hair was sparse, and the skin smooth and velvety. There was slight cyanosis of the lips and nail beds, the palms were rosy and there were peculiar erythematous patches on the arms that appeared and disappeared. The genitalia appeared normal. Except for the discharging sinus in the upper jaw, slight hypertension, 150–176/76–84, and the changes shown in the roentgenogram of the skull, there were no other evidences of organic disease. His blood sugar curve proved to be normal and a salt withdrawal test disclosed no evidence of adrenocortical insufficiency. His anorexia proved to be intractable. September 3 he had definite dependent edema. He was given 0.03 Gm. of thyroid daily on August 29. On September 3 and 4 this was increased to 0.06 Gm. It had no objective effects, but he said he felt as if things were going faster. Thyroid was stopped on September 9 because of recurrence of a diarrhea which he had had at intervals, with transient fever. Thyroid was not resumed because the patient insisted that it would aggravate his loss of weight.

Case 6 (*B74923*) *C. V.*, male, born in 1917, was seen first on December 7, 1945, complaining of impotence. His spinal fluid is said to have been xanthochromic and x-ray

examination of the skull revealed erosion of the sella turcica and increased convolutional markings. In February, 1946, his blood sugar tolerance curve up to five hours was normal, but basal metabolism, SPI and urinary ketosteroids were all greatly reduced. He was therefore given 0.06 Gm. of thyroid daily without evident effect. At this time he had signs of hypogonadism, but glucose tolerance curves were normal. On six different occasions between March 12, 1946 and May 10, 1947 serum chloride and bicarbonate were within normal limits.

Case 7 (*B69216*) *A. T.*, male, born in 1901, had sustained at birth an injury that resulted in clumsiness and disability of the left hand. At age 14, over the course of a year, he gradually lost the sight of his right eye. His testes never developed to full size and he never attained any facial or body hair. Beginning in 1918, he experienced attacks of weakness while straining at stool (he was constipated). Twice in the year preceding his admission to the New Haven Hospital (May 16, 1945) he had been admitted to other hospitals for collapse, pulseless, with low blood pressure. These attacks were usually relieved by sugar. When he was admitted to the New Haven Hospital he was recovering from a respiratory infection with a cough of three weeks' duration. His skin was white and soft, but not particularly moist. He had no beard nor body hair. There was a right external strabismus, atrophy of both optic nerves, a defect in the left superior temporal visual field, a left hemiparesis, underdeveloped genitalia and rales over the bases of his lungs. On May 20 he had an attack characterized by difficulty in breathing, a feeling of constriction in his chest and general weakness. On May 22, 50 cc. of fluid were removed from the right chest and 250 cc from the left. Subsequent x-ray examination revealed enlargement of the left ventricle and left hydropneumothorax. The latter gradually cleared up while he was in the hospital. On May 30 he was given 0.06 Gm. of thyroid daily. June 1 a salt-poor diet was prescribed, but that morning serum chloride proved to be only 84.4 mEq. per liter with bicarbonate 25.5 mEq. June 4 he was given 10 Gm. of NaCl and 5 mg. of DOCA daily. On June 14 the latter was increased to 7 mg. On this regimen serum chloride rose to normal. June 29, pellets of DOCA were implanted. Meanwhile, on June 18, the dose of thyroid had been increased to 0.12 Gm. daily. For a time after this he had edema, which was controlled by reduction of extra salt which he was taking. The subsequent course is shown in the tables. DOCA implants were renewed early in May, 1946 and in November, 1948.

Case 8 (*99362*) *C. J.*, male, born in 1900, in 1943 to 1944 noticed progressive weakness and loss of potency, together with a loss of body hair and daily hot flashes. In 1939, when a papilloma was removed from his bladder, an anemia was discovered which persisted despite iron and folic acid. Subsequent to the operation he lost about 15 pounds. When first seen, June 10, 1947, he appeared pale and somewhat thin, with sparse body hair, pulse 72, and blood pressure 105/80. The eyegrounds were normal. There were crackling rales at both bases, the testes were atrophic. His urine was normal. He had a moderate secondary anemia. A roentgenogram of the skull revealed enlargement of the sella turcica. Visual fields were normal. In October he was admitted to the hospital for evaluation. He developed no hypoglycemia in the course of a 5-hour glucose tolerance test; but, when salt was restricted, the serum sodium fell rapidly to 118 mEq. per liter, the blood pressure to 94/64 and he went into collapse. This condition was not controlled by methyl testosterone, so DOCA pellets were implanted on October 27. These were renewed on November 20, 1948. The SPI, initially low, rose between September and October, 1947, from 2.9 to 5.1 γ per cent without special therapy. At the time of the high figure the serum cholesterol was also elevated. No explanation for this paradoxical re-

action was discovered. Subsequently the SPI fell again to hypothyroid levels, where it remained despite 0.03 Gm. of thyroid and 0.03 Gm. of methyltestosterone daily. The basal metabolism, however, rose and the cholesterol fell, to normal figures. In November, 1948, he was given for three days 0.12 Gm. of thyroid daily without any effect upon SPI. There was a diminution of serum cholesterol of somewhat uncertain significance.

Case 9 (*A79550*) *F. T.*, male, born in 1920, in February 1938, noted blurring of vision in his right eye, not relieved by glasses, and occasional headaches. When admitted to the hospital on July 15 he had atrophy of the right optic nerve, a slight lateral strabismus, and a left temporal hemianopsia. He was beardless, but his genitalia seemed normal. X-ray examination revealed enlargement of the sella turcica, particularly the left side, with atrophy of the left posterior clinoid process and the dorsum. July 28 a cyst was excised from the sella turcica. He was readmitted to the hospital on February 7, 1940, completely blind in the right eye and with a complete macula-sparing hemianopsia on the left. X-ray examination showed that the clips anterior to the sella had separated, suggesting an expanding lesion in this region. He was again admitted October 30, 1945, because of somnolence, fatiguability, further loss of vision, spells of forgetfulness and anorexia. There was 2+ papilledema in the left eye. Bone age did not appear to be delayed. A second operation was performed with further removal of the tumor substance. In 1946, when the urinary ketosteroids were reported to be 10.2 mg. per day, urinary cortins were 0. Nevertheless serum electrolytes and blood sugar were normal. Early in 1947 his vision again began to deteriorate. July 21 he had a left temporal hemianopsia and the visual acuity in the left eye was reduced to 15/200. August 4 the visual fields had become further restricted. He was, therefore, readmitted to the hospital. On August 13 craniotomy was again performed, and 150 to 200 cc. of fluid was withdrawn from a cyst arising in the region of the sella. The cyst was then excised as far as possible. The temperature rose sharply to 106.4 after the operation and the blood pressure became unobtainable. He improved rapidly, however, in the course of the next twelve hours. Recovery was uncomplicated after the first four days, except that he developed a slight infection of his wound and a saphenous thrombophlebitis. The vision seemed definitely improved; but by March 1, 1948, it had deteriorated again and by October 8 his mental state had also deteriorated. October 14 another craniotomy was performed. A suprasellar cyst was again aspirated and excised. The blood pressure was well sustained without special treatment. Recovery was again complicated by a thrombophlebitis. On one occasion, after the 1947 operation, he was suspected of having an acute diabetes insipidus; but in 1948 urines were normal, with specific gravities of 1.023 and 1.016. When seen on March 25, 1949, his chief complaints were obesity, somnolence and lack of energy. His skin felt rather dry and, although the room was warm, on taking off his clothes his skin became covered with goose-pimples. His pulse was 62, and blood pressure 128/98. He had little hair on his face, but his voice and genitalia were those of an adult male. The tumor was identified as a chromophobe adenoma.

Case 10 (*C20693*) *M. S.*, female, born in 1892, in 1945 noticed bilateral impairment of temporal vision and slight diplopia, which were not relieved by glasses. The menopause occurred without symptoms the same year. Beginning in 1946 she developed nocturia once a night. In 1947 she began to suffer from episodes of slight dyspnea with wheezing respirations, attributed to asthma and relieved by pills. During 1948 she lost 15 pounds without symptoms other than fatiguability. When admitted to the hospital January 3, 1949, she was well developed, slightly obese, with a pulse rate of 80 and blood pressure 130/80. Her skin was normally moist and soft, her breasts were well developed,

and the thyroid was not palpable. She had a complete bitemporal hemianopsia with general diminution of vision in the left eye. The nasal portion of the left optic disc was pale. Neurologic examination revealed nothing abnormal otherwise. Transient wheezes were audible over her chest and a soft liver edge was felt 3 to 4 cm. below the costal margin. The spleen was not palpable. A roentgenogram revealed thinning of the dorsum sellae and both posterior clinoid processes. An arteriogram showed that the left common-carotid and anterior cerebral arteries were displaced upward and outward. Basal metabolism was normal, but SPI was distinctly reduced and cholesterol was elevated. A prolonged glucose tolerance test gave normal results. With moderate salt restriction (about 5 Gm. daily) serum sodium fell from 137 to 129 mEq. per liter; but she had no untoward symptoms and the excretion of sodium chloride in the urine fell. January 19 she was given 0.03 Gm. of thyroid, which was increased to 0.12 Gm. the next day, when she was discharged from the hospital.

She was readmitted February 27, unchanged except for a mild coryza. March 2 craniotomy was performed. A solid tumor was removed from the region of the optic chiasm. That night she had a severe epistaxis and at 4 A.M. the next morning became unresponsive, with a blood pressure of 100/60, pulse 80 and a temperature of 101.2. She had received saline infusions and adrenal cortical extract since operation. An extra dose of extract was given. She recovered rapidly. It seems doubtful whether the collapse was due to cortical insufficiency. The serum electrolytes next morning were normal. Her cerebrospinal fluid pressure proved to be considerably elevated and her temperature continued to rise to 103.2 (presumably because of a postoperative pneumonia). The combination of these complications and the massive epistaxis was enough to explain a transient collapse. The temperature fell rapidly to normal on March 5 and recovery thereafter was uncomplicated. At the time of discharge on March 11 her vision was almost completely restored. The tumor proved to be a chromophobe adenoma.

Case 11 (*C21235*) *G. G.*, female, born in 1917, had noticed enlargement of both hands and feet and increasing headaches during the preceding year. Her menses had not changed. Her features suggested acromegaly and her hands and feet were unusually large; but x-ray examination did not disclose true stigmata of acromegaly. The sella turcica appeared normal and there were no signs of increased intracranial pressure. Vision was normal. Glucose tolerance and salt restriction tests also gave normal results.

Case 12 (*C21335*) *S. J.*, female, born in 1907, was referred to the hospital because an x-ray examination of the skull had revealed striking enlargement and erosion of the sella turcica. No anatomic nor functional evidences of intracranial tumor were discovered. There were no stigmata of hypothyroidism. Her primary complaint had been pain in the flank which proved transient, but inexplicable. SPI on January 21 proved absurdly high, because she had had roentgenograms of both gall-bladder and urinary tract about four weeks earlier. Cholesterol was somewhat elevated.

Case 13 (*C22269*), *G. B.*, female, born in 1930, in August 1948, began to suffer from bilateral temporal headaches, accompanied by nausea and anorexia, and from progressive lethargy and loss of energy. December 25 she noticed transient diplopia. This recurred on January 27, 1949, this time persisting and accompanied by infra-orbital pain, and paresthesias of the face and mouth. January 31 her vision suddenly diminished, especially in the left eye. February 8, on awaking, she found the right eye totally, and the left eye almost totally, blind. Her menses continued to be regular and normal. When she entered the hospital on February 10, she was totally blind in the right eye and the vision

of the left was greatly impaired. There was a paralysis of the right external rectus muscle. The optic discs were flat. The heart sounds could be heard over the temples, louder on the right side. Pupillary reflexes were not obtained in the right eye, but both direct and consensual reactions were elicited in the left. There was analgesia of the left infra-orbital region. X-ray examination revealed prominent convolutional markings in the skull and considerable enlargement of the sella turcica with atrophy of both anterior clinoids, the tuberculum sellae, posterior clinoids and the dorsum sellae. The partition between the sella and the sphenoid sinus also appeared to have been destroyed. Arteriograms revealed displacement of the internal carotids. Ventriculograms revealed elevation of the floor of the third ventricle. A right frontal craniotomy was performed on February 23. A large cyst in the region of the optic nerves was aspirated and injected with pantopaque. Subsequent roentgenograms revealed an enormous cyst extending into the nasopharynx and paranasal sinuses. Section of a portion of the tumor proved that it was a chondroma arising from the sphenoid. Her recovery from operation was uneventful. The vision in the left eye has improved greatly. Because the arteriogram was taken before chemical examinations of the blood were made, SPI could not be measured. No evidences of ovarian or adrenocortical deficiencies were discovered.

Case 14 (*C6180*) *F. H.*, male, born in 1925, in November of 1947 noticed drooping of his left upper eyelid. At the same time he began to suffer from nocturnal attacks of pain in the left orbit and occasionally in the left superior maxilla, of variable duration, associated with conjunctival injection. He had been quite thin until 1942. Between this time and the onset of the symptoms noted above he gained 60 pounds. In 1943, because his basal metabolism was found to be −23 per cent, he took thyroid for about seven months. When admitted to the hospital on January 11, 1948, he did not appear ill. He was definitely obese, but the texture and moisture of his skin were normal. There was a distinct ptosis, weakness of convergence and slight dilatation of the pupil in the left eye. Otherwise the physical examination was unimportant. Lumbar puncture revealed a spinal fluid under a pressure of 180 mm., with normal dynamics, a negative Pandy, but 74 mg. per cent of protein and 600 crenated red blood cells per cubic millimeter. It was suspected that he had an intracranial aneurism, but an arteriogram revealed only straightening and elevation of the distal end of the left internal carotid artery. The sella turcica was enlarged and the anterior clinoid process was elevated. The urine on admission contained 20 to 30 red blood cells per high power field, but rapidly cleared. This remained unexplained. Tests of renal function and intravenous pyelograms were normal. It was presumed that he had a chromophobe adenoma of the pituitary gland. Under x-ray therapy to the pituitary, the muscular weakness and vision of the eye improved greatly. No evidences of hypofunction of thyroid, adrenals or gonads were found.

Case 15 (*B99513*) *M. B.*, female, born in 1897, about January, 1947, noted some impairment of vision. In May there was distinct fogginess in the vision of the left eye. At this time a defect of the left temporal field was detected. In the middle of June she began to have mild headaches at intervals. Since 1937, when her menses suddenly ceased, she had suffered from extreme nervousness and intense hot flashes. When she entered the hospital on July 8, 1947, the only important physical finding was the defect in the left temporal field, mentioned above. X-ray examination of the skull revealed evidences of increased intracranial pressure, destruction of the posterior clinoid processes and the dorsum sellae, with widening of the sella turcica. X-ray treatment was of no benefit. By October she had a bitemporal hemianopsia and a small nasal defect in the left field. She was, therefore, readmitted to the hospital on November 17 and on November 19 a cra-

niotomy was performed and the tumor was removed. It proved to be an adenoma, probably originating from the pars intermedia. Following the operation her vision improved greatly. She had no clinical signs of hypothyroidism or adrenal cortical insufficiency.

Case 16 (*A99433*) *M. S.*, female, born in 1916, in July 1935, suddenly ceased to menstruate. At the same time severe hot flashes began, which were treated during the first two years with injections of estrogens. In the summer of 1938 the vision in her right eye began to fail. In October 1939, this process suddenly became accelerated and she had occasional brief occipital headaches. When she was admitted to the hospital on January 8, 1940, she had almost complete loss of vision in the right eye, with atrophy of the optic nerve and a temporal hemianopsia of the left eye. The physical examination was otherwise unimportant. X-ray examination of the skull revealed destruction of the posterior clinoid processes and the dorsum sellae. With the assumption that she might have a chromophobe adenoma, x-ray therapy to the pituitary was instituted. The vision improved strikingly under this treatment. The sight in the left eye was almost completely restored and there was perceptible improvement of the right eye. The amenorrhea and hot flashes, however, continued. Furthermore, this improvement has been maintained without further therapy. On April 13, 1949, her right eye was still practically useless and amenorrhea persisted, with occasional hot flashes. The only other significant complaints were nervousness and lack of energy, which, she insisted, were worse in the winter than in the summer. She was doing skilled work steadily in a part-time job and, in the summer, enjoyed active physical exercise, especially swimming. She had never experienced any acute attacks of weakness or collapse. She looked well. The skin was soft, smooth, and normally moist. The breasts were well developed and seemed to contain the normal amount of glandular tissue. Her pulse rate was 84, and blood pressure 108/80. Her blood count and urine were normal.

Case 17 (*A52397*) *K. D.*, female, born in 1876, had 3 pregnancies. Two were normal, but the third in 1918 ended in a miscarriage near term, complicated by a peritonitis requiring laparotomy. She had a symptomless menopause in 1933. She lived a vigorous life in good health until the summer of 1935 when she began to have occasional attacks of epigastric distention, nausea and vomiting. In August 1936, increasing nervousness and irritability appeared. September 24 persistent nausea and vomiting with fever set in. An ovarian cyst, which had partially obstructed the sigmoid, was removed. Recovery was uneventful. September 26, 1945, she was again admitted to the hospital, having lost 20 pounds in the two preceding years. During this period she had noted increased fatiguability, deepening of her voice and trembling of the right hand, which for one year had been accompanied by polyuria and polydypsia. Her urine was found to contain albumin and sugar. Her blood pressure was low and her pulse rapid. Insulin was required to control the glycosuria. She was readmitted July 29, 1946, because of continued tremor of the right hand, progressive weakness and nausea. X-ray examination of the skull somewhat earlier had revealed an enlarged sella turcica for which she was given x-ray therapy to the pituitary in January, 1946. There were no skeletal stigmata of acromegaly. Her pulse was again rapid and her blood pressure low. Nutrition was fairly well preserved. From this time on, her condition deteriorated rapidly. Her appetite failed, she suffered from nausea and became increasingly weak and emaciated. She developed a state of extreme agitation and restlessness which was aggravated by rectal prolapse which had followed a hemorrhoidectomy performed in 1940. The diabetes meanwhile improved, so that in 1948 she was able to stop taking insulin. At this time also her blood pressure rose to the normal level. No definite signs of any advance of the intracranial lesion were demon-

strated by either x-ray or physical examination, except a transient concentric contraction of the visual fields of questionable significance. She is suspected of having an eosinophilic adenoma of the pituitary gland. Her thyroid gland has never been palpable.

Case 18 (*B96690*) *F. P.*, female, born in 1935, at the age of 3.5 years developed enuresis. In 1944 to 1945 polydipsia and polyuria appeared. At the end of 1946 she noticed blurring of vision and a staring expression of the left eye was observed. In October 1947, rhythmical motions of the eyes, especially the left, appeared. When seen on April 29, 1947, she was underdeveloped, only 52.5 inches in height and weighing 62 pounds. She was pale, with smooth, soft skin and no secondary sex characteristics. The left pupil was larger than the right and this eye diverged. There was a constant vertical nystagmus, especially of the left eye, and striking impairment of vision with bitemporal hemianopsia, but her eyegrounds were normal. X-ray examination revealed asymmetrical enlargement of the sella turcica with erosion of the dorsum sellae. May 7 a craniotomy was performed and a craniopharyngioma cyst was, as far as possible, extirpated. The nystagmus disappeared after the operation, but her divergent squint and diabetes insipidus persisted. The latter was incompletely controlled by insufflation of posterior pituitary powder. In addition she was given 0.03 Gm. of thyroid daily.

Case 19, *A. A.*, female, born 1922, in 1946 developed an acute spontaneous pneumothorax. Just as she was recovering from this episode, extreme polyuria and polydipsia suddenly appeared. She had no other symptoms or signs. She was treated in a sanatorium for a year and subsequently placed on a regimen of restricted activity because of the suspicion of pulmonary tuberculosis, although this diagnosis was never established by positive evidence. On this regimen her weight, which fell from 120 to 98 pounds immediately after the pneumothorax, rose to 168.5 pounds. When seen March 4, 1948, she appeared the picture of health, though far over her proper weight. She was vivacious, her skin was normal in color, texture and moisture. Her thyroid was slightly enlarged, and her pulse was 90. She had an unmistakable diabetes insipidus with a urine specific gravity of only 1.001. This responded most satisfactorily to insufflation of posterior pituitary powder. Because of the low SPI she was given 0.03, and then 0.06 Gm. of thyroid daily. This had no demonstrable effect, although SPI rose. Thyroid had been discontinued for about two months before the last observation.

Case 20, *H. E.*, female, born in 1930, belongs in an entirely different category. She was first seen in 1946 at which time she had the appearance of a child 8 to 10 years old; her weight was only 33.9 Kg. and her height 116.3 cm. She had never menstruated and presented no secondary sexual characteristics. Except for rheumatic fever following measles at the age of 4 years, she had enjoyed excellent health. No evidences of visceral disease of any kind could be found. X-ray examination revealed a normal skull, but her epiphyses were generally ununited. She was treated, as the table indicates, with thyroid and, for a short period, with methyltestosterone. Her height on January 25, 1948, had increased to 139 cm. and her weight to 38.6 Kg., but her infantile appearance and amenorrhea persisted.

THE EFFECT OF TESTOSTERONE PROPIONATE ON METASTASES TO BONE FROM CARCINOMA OF THE BREAST

FREDERICK W. PRESTON, M.D., SAMUEL G. TAYLOR, III, M.D. AND JOSEPH L. CRUMRINE, M.D.

From the University of Illinois Research and Educational Hospitals and the Presbyterian Hospital, Chicago, Illinois

THE effect of sex hormones on advanced female breast cancer has been studied by Adair (1, 2), Farrow (3, 4), Nathanson (5–9), Haddow (10) and others (11–20) and has been the subject of two group studies, one conducted by the Royal Society of Medicine (21, 22) and the other, still in progress, by the Therapeutic Trials Committee of the Council on Pharmacy and Chemistry of the American Medical Association (23). We have participated in the latter of these two studies and our observations on 70 patients have previously been reported (19).

Among 50 female patients with advanced breast cancer, to whom we have given androgens, there were 17 with metastases to bone who received large doses of testosterone propionate. All of these patients were markedly masculinized. Twelve of the patients are now dead. Because of the striking palliation afforded some of these patients, the group is of special interest and forms the basis of the present report.

The ages of the patients at the time of beginning treatment varied from 31 to 60 years. Bone metastases frequently affect younger patients as emphasized by Farrow and Woodard (4). The average age of our patients when bony metastases developed was 46 years, whereas the average age of 50 of our female patients who had carcinoma of the breast with metastases to soft tissue only, was 57 years.

In 14 of the 17 patients the lesions occurred after mastectomy, and 3 patients had an advanced primary lesion when they first came under our observation. All of the cases were beyond the hope of surgical cure.

Roentgen therapy to the site of the primary lesion has been given to 2 of the patients who had inoperable primary lesions and postoperatively to all but 2 patients who had mastectomy. Androgen therapy was withheld until six weeks or more after the last roentgen treatment, in all except 2 patients who received roentgen therapy to isolated bone metastases for a short time in conjunction with androgen therapy. These patients were included in the study because subsequently they received sufficient androgen therapy so that its effect alone could be evaluated. In neither of

Received for publication May 7, 1949.

these patients was there roentgenologic evidence of regression of bone metastases, in spite of the combined therapy which they received.

During the period of androgen administration, no other medication of importance was given the patients except analgesics to control pain, and teropterin (pteroyltriglutamic acid) to 2 patients in the hope of affording them some additional palliation. Teropterin had previously been shown to have no effect on primary or metastatic carcinoma of the breast (24). In some cases, female sex hormone had been previously given to these patients but with one exception it was not used during the period of androgen therapy.

Recurrence or soft tissue metastases were present in all of these patients. Usually both soft tissue and bone metastases were present when androgen therapy was started. However, in 1 patient four years elapsed, and in another, one year, between the time of appearance of bone metastases and the development of soft tissue metastases.

Serum calcium determinations made at frequent intervals in all these patients failed to reveal an increase of the serum calcium content above normal limits (9 to 12 mg. per 100 cc. of serum) except in 3 patients. Hypercalcemia was exceptional even when widespread bone involvement existed. Two patients who had hypercalcemia at the onset of androgen therapy seemed to deteriorate rapidly during the therapy. A third patient developed hypercalcemia while on androgen therapy and thereafter her condition rapidly deteriorated and the therapy was omitted.

In 15 patients the serum calcium was within normal range at the onset of androgen therapy. No further changes in serum calcium, except in the patient mentioned above, were demonstrated on repeated examinations either during therapy or after it was discontinued.

The dose of testosterone propionate varied from 150 to 700 mg. a week, given in three to seven divided doses. The dose most frequently used was 100 mg. given intramuscularly three times a week, since this seemed to be the optimum dose for most patients. However, some patients seemed to require more, and in one, improvement was noticeable shortly after her dose was increased from 300 to 700 mg. weekly. In 3 patients, testosterone pellets were implanted into the fatty tissues overlying the anterior rectus fascia. The total amount of testosterone propionate varied from 1.7 Gm. administered over a five-week period to one patient to 28.5 Gm. given over an eleven-month period to another.

The diagnosis of carcinoma metastatic to bone was established roentgenologically in all patients studied. Bone surveys consisting of views of the entire spine in two planes and anterior-posterior views of the ribs and pelvis were made at one-month to three-month intervals during therapy. Views of the skull and long bones were made in all patients whose symp-

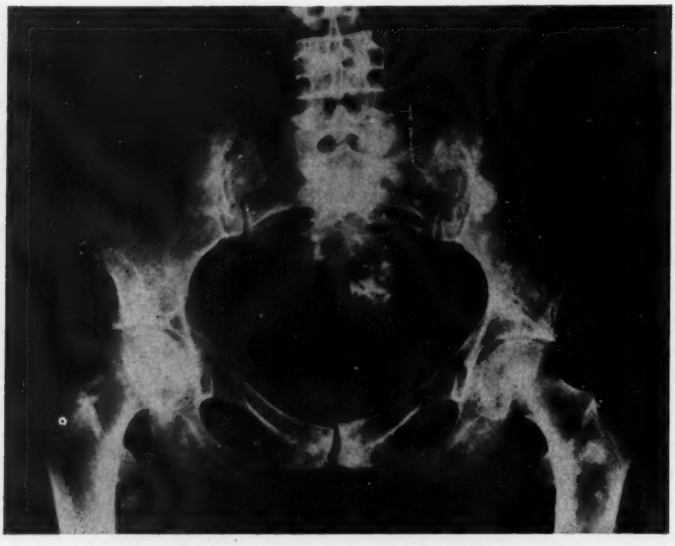


FIG. 1. Osteoplastic metastases in the pelvis and left femur of a 54-year-old woman.

FIG. 2. The same patient as in Figure 1 after fifteen months of testosterone therapy. Decalcification of the lesions was apparent after approximately 5.2 grams of testosterone given during a 5½-month period, and further decalcification occurred as shown above. The patient experienced complete relief from pain in her pelvis. She became markedly masculinized.

toms suggested that lesions might be present in these regions. In 2 patients, there occurred regression of bone metastases to such an extent that the lesions no longer could be seen on roentgenograms. These patients at the present time are in good condition and are still receiving therapy (Figs. 1 and 2).

A third patient had an osteolytic lesion in the second lumbar vertebra which recalcified to such an extent that it appeared from the roentgenograms that it might have completely regressed. However, at autopsy, con-

FIG. 3. Osteolytic metastasis in the body of the second lumbar vertebra, producing pathologic compression fracture. The patient was 37 years old.

siderable viable tumor tissue was still present in the lesion (Figs. 3 and 4). A fourth patient had an osteolytic lesion in the proximal portion of the left femur which recalcified during androgen therapy. When regression (recalcification of osteolytic lesions or decalcification of osteoplastic lesions) was observed to take place, the changes were not apparent roentgenologically until at least three months after starting therapy. The 4 patients in whom these favorable changes occurred were all markedly masculinized when regression was first observed. These patients had received 3,500, 5,200, 5,300 and 8,400 mg. of testosterone propionate respectively, before any regression of their bone lesions first was demonstrated.

The status of these patients at present is as follows: 12 are dead; 1 is

living but is in a terminal condition; 3 are in relatively good condition but have widespread soft tissue metastases which still seem to be in check; and 1 is in good condition but has small recurrences in the skin. The fact that only 5 patients are still alive after two years of this study again emphasizes that the treatment is not curative. Of the 5 patients still living, all have experienced marked palliation of symptoms, and of those who are now dead, some palliation was afforded to 6. There was either relief of pain

FIG. 4. Recalcification of the lesion shown in Figure 3 after four months of androgen therapy. Recalcification was first apparent after the patient had received 8.4 grams of testosterone propionate over a fourteen-week period. This patient is now dead; however, she received considerable relief of symptoms from the therapy for over a year, during which time she was given 28.5 grams of the drug. She was markedly masculinized.

associated with the metastases, or temporary improvement in soft tissue lesions, or subjective improvement so that the patient stated she felt better. Usually these palliative effects occurred in combination. Of the patients who are now dead, 3 died from pulmonary metastases and 9 from widespread carcinomatosis and cachexia.

There were 5 patients in the entire group herewith reported who experienced no benefit whatsoever from androgen therapy. In these cases the

drug was administered over a sufficient length of time to eliminate the possibility of inadequate trial.

Masculinization was apparent in these women. Recurrences in the skin progressed rapidly in 2 of them in spite of androgen therapy. In 1 patient, hypercalcemia was present which seemed to regress when androgens were omitted. In 3, visceral metastases extended rapidly in spite of the drug.

Pain was associated with metastases to bone in 14 of the 17 patients. In general, the degree of pain corresponded to the extent of the lesion. However, there were 2 patients with rather extensive bone metastases who had no pain and 2 others who had single small lesions which were painful. Lesions of the ribs and vertebrae were painful in all cases, whereas 1 patient with involvement of the sternum and 3 with metastases to the pelvis had no pain from these lesions. The character of the pain usually was a dull continuous ache, severe enough at night to interfere with sleep. Twelve of the 14 patients with bone pain (85 per cent) experienced relief with androgen therapy. Usually improvement was noticed within seven to fourteen days after beginning treatment. In some cases the duration of relief was short and in others it was much longer. One patient with a localized metastasis to the body of the fifth thoracic vertebra has been free of pain for one year (Figs. 5 and 6). Another patient with extensive lesions in the pelvis has had relief of pain for nineteen months except for periods of time when the drug has been discontinued. Her pain recurs about one week after the therapy is omitted but again improves within ten days after therapy is started.

In all cases in which regression of bone lesions was demonstrated by roentgenogram, the pain associated with these lesions was improved. However, 1 patient who had intercostal pain which we attributed to an osteolytic metastasis in a rib, continued to have pain after the metastasis could no longer be demonstrated roentgenologically.

Pain was also an important symptom in 3 patients in whom an hypercalcemia was present. In 2 of these patients, some relief of pain occurred even while their general condition was deteriorating.

DISCUSSION

That calcium content of the serum in patients with metastases to bone varies within wide limits has been noted by several authors (1, 4, 25, 26). From our own observation of these patients, a serum calcium level above 12 mg. per 100 cc. indicates extensive metastases of an osteolytic variety. Three of our patients had this finding, and all failed to tolerate androgen therapy in the doses used. Tachycardia, persistent nausea and vomiting and weakness were present. There was some improvement in these symptoms when the androgen was omitted. The serum calcium levels dropped

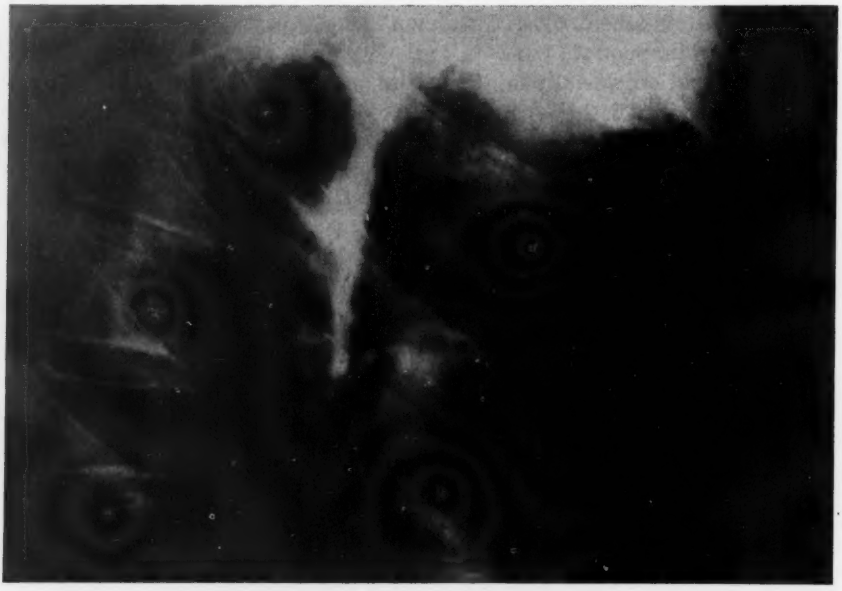


FIG. 5. Osteolytic metastasis of the fifth thoracic vertebra of a 43-year-old woman.

after the drug was omitted in 2 patients, and in 1 there was later a further rise. Adair and Herrmann (2) also observed a patient with hypercalcemia whose condition was aggravated by androgen administration and who showed improvement when the therapy was stopped. When the drug was continuously given in smaller doses a second rise in serum calcium occurred which again regressed when the drug was withheld. Farrow and Woodard (4) noted a favorable response when androgens were discontinued in 3 patients with hypercalcemia, 1 of whom had hypercalcemia when therapy was started. It would, therefore, seem that hypercalcemia is a contraindication to androgen therapy, which was the conclusion reached by Adair and Herrmann. It is of interest that none of our patients, in whom the serum calcium rose above normal, was ambulatory. This was also observed by Herrmann (27).

Amenorrhea was present in all patients during therapy. Masculinization, characterized by a lowering of the pitch of the voice, hirsutism with male distribution of facial and pubic hair, male development of body musculature, and increase in the size of the clitoris was present to at least some degree in all. Other manifestations included acne and increased libido which sometimes was a source of annoyance especially in older patients. Growth of hair on the upper lip and acne were causes for complaints in

some patients, but, in general, masculinization seemed to be well accepted as a small price to pay for the relief of pain. One of our patients developed cardiac decompensation characterized clinically by shortness of breath and dependent edema, and we have seen other patients become seriously decompensated and manifest sodium retention on large doses of testos-

FIG. 6. The same lesion as shown in Figure 5 after the patient had received 15 grams of testosterone propionate over a twelve-month period. During this time the metastasis gradually increased in size. Compression fracture of this vertebra is imminent unless her spine is supported by a brace. She was markedly masculinized, and, because she received complete relief of a severe pain associated with this lesion, the therapy was considered worthwhile.

terone propionate. This was controlled by the frequent use of mercurial diuretics and low sodium diet.

The greatest benefits of the drug are the relief of pain which occurred in 85 per cent of our patients, and regression of certain bone lesions which occurred in 25 per cent. Other beneficial effects include an increase in appetite, gain in weight, and an increase in sense of well being. It is significant that the patients who received the greatest benefit from the

therapy were those who received the largest doses of the drug over the longest period.

SUMMARY

Testosterone propionate in amounts varying from 1.7 to 28.5 grams was given to 17 female patients with carcinoma of the breast metastatic to bone, for periods of from 5½ to 78 weeks. Masculinization occurred in all.

Regression of bone metastases was observed in 4 patients (25 per cent). These patients showed ability to tolerate the drug in large doses for long periods of time. Osteoplastic metastases were observed to decalcify and osteolytic metastases were observed to recalcify.

Complete disappearance of bone metastases roentgenologically was observed in 2 instances.

The serum calcium levels remained within normal limits in 14 of 17 patients given large dose of androgens.

In 3 patients the bone metastases were accompanied by hypercalcemia and these patients tolerated androgen therapy poorly, suggesting that when hypercalcemia is present in bedridden patients androgens are contraindicated.

Twelve of 14 patients (85 per cent) whose metastases were painful obtained relief for periods varying from one to eighteen months. Some patients continue to experience relief of pain from bone metastases even though there is roentgenologic evidence that the metastases are progressing.

Although 12 of the 17 patients died of their disease, worthwhile palliation was afforded to all but 5.

REFERENCES

1. ADAIR, F. E.: The use of the male sex hormone in women with breast cancer, *Surg., Gynec. & Obst.* **84**: 719–722, 1947.
2. ADAIR, F. E., and HERRMANN, J. B.: The use of testosterone propionate in the treatment of advanced carcinoma of the breast, *Ann. Surg.* **123**: 1023–1035, 1946.
3. FARROW, J. H.: The effect of sex hormones on skeletal metastases from breast cancer, *Surgery* **16**: 141–151, 1944.
4. FARROW, J. H., and WOODARD, H. Q.: The influence of androgenic and estrogenic substances on the serum calcium in cases of skeletal metastases from mammary cancer, *J.A.M.A.* **118**: 339–343, 1942.
5. NATHANSON, I. T.: The relationship of hormones to diseases of the breast, *Surgery* **16**: 108–140, 1944.
6. NATHANSON, I. T.: Endocrine aspects of cancer, *New England J. Med.* **231**: 764–769, 795–901, 1944.
7. NATHANSON, I. T.: Influence of stilbestrol on advanced cancer of breast, *J. Clin. Investigation* **25**: 930, 1946.
8. NATHANSON, I. T.: The effect of stilbestrol on advanced cancer of the breast, *Cancer Research* **6**: 484, 1946.

9. NATHANSON, I. T.: Hormonal alteration of advanced cancer of the breast, *Surg. Clinics North America* **27**: 1144–1150, 1947.
10. HADDOW, A.; WATKINSON, J. M., and PATTERSON, E.: Influence of synthetic estrogens upon advanced malignant disease. *Brit. M. J.* **2**: 393, 1944.
11. BOGER, W. P.: Methyl testosterone and surgical castration in the treatment of carcinoma of the breast, *J. Clin. Endocrinol.* **6**: 88–98, 1946.
12. FELS, E. J.: Treatment of breast cancer with testosterone propionate: a preliminary report, *J. Clin. Endocrinol.* **4**: 121–125, 1944.
13. HERRMANN, J. B., and ADAIR, F. E.: The effect of testosterone propionate on cancer of the female breast with soft tissue metastases, *J. Clin. Endocrinol.* **6**: 769–775, 1946.
14. HERRMANN, J. B.; ADAIR, F. E., and WOODARD, H. Q.: The use of testosterone propionate in the treatment of advanced carcinoma of the breast. II. The treatment of osseous metastases, *Surgery* **22**: 101–119, 1947.
15. HERRMANN, J. B.; ADAIR, F. E., and WOODARD, H. Q.: The effect of estrogenic hormone on advanced carcinoma of the breast, *Arch. Surg.* **54**: 1, 1947.
16. LOESER, A. A.: Mammary carcinoma—response to implantation of male hormone and progesterone, *Lancet* **2**: 698–700, 1941.
17. MCCULLAGH, E. P.: The use of sex hormones in cancer, *Cleveland Clinic Quarterly* **16**: 21–32, 1949.
18. SCHWANDER, H., and MARVIN, H. N.: Treatment of carcinoma of the human breast with testosterone propionate: a report of five cases, *J. Clin. Endocrinol.* **7**: 423–432, 1947.
19. TAYLOR, S. G. III.; SLAUGHTER, D.; SMEJKAL, W.; FOWLER, E. F., and PRESTON, F. W.: The effect of sex hormones on advanced cancer of the breast, *Cancer* **1**: 604–617, 1948.
20. ULRICH, P.: Testostérone (hormone mâle) et son rôle possible dans le traitement de certains cancers du sein, *Acta, Union internat. contre cancer* **4**: 377–380, 1939.
21. Discussion on advanced cases of carcinoma of breast treated by stilbestrol, *Proc. Roy. Soc. Med.* **37**: 731–736, 1944.
22. Report of Section on Radiology: Royal Society of Medicine. *Brit. M. J.* **2**: 20, 1944.
23. Council on Pharmacy and Chemistry: Estrogens and androgens in mammary cancer, *J.A.M.A.* **135**: 987–989, 1947.
24. TAYLOR, S. G. III.; SLAUGHTER, D.; CRUMRINE, J. L.; HASS, G., and PRESTON, F. W.: The effect of antifolic acid derivatives on patients with far-advanced carcinomatosis, *Proc. Central Soc. Clin. Research.* **21**: 92, 1948; and *J. Lab. & Clin. Med.* **33**: 1645, 1948.
25. GUTMAN, A. B.; TYSON, T. L., and GUTMAN, E. B.: Serum calcium, inorganic phosphorus and phosphatase activity in hyperparathyroidism, Paget's disease, multiple myeloma and neoplastic disease of bone, *Arch. Int. Med.* **57**: 379–413, 1936.
26. WOODARD, H. Q., and HIGINBOTHAM, N. L.: The correlation between serum phosphatase and roentgenographic type in bone disease, *Am. J. Cancer* **31**: 221, 1937.
27. HERRMANN, J. B.: KIRSTEN, R., and KRAKAUER, J. S.: Hypercalcemic syndrome associated with androgenic and estrogenic therapy, *J. Clin. Endocrinol.* **9**: 1–12, 1949.

THE TREATMENT OF ADDISON'S DISEASE BY THE INTRAORAL ADMINISTRATION OF DESOXYCORTICOSTERONE ACETATE TABLETS

EVELYN ANDERSON, M.D., PH.D.,* LAURANCE W. KINSELL, M.D., TROY C. DANIELS, PH.D. AND EDWARD HENDERSON, M.D.

From the Division of Medicine and College of Pharmacy, University of California, San Francisco, and the Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey

MANY substances are effectively absorbed through the oral mucosa, as has long been known to physicians; but until recently this route of administration has been used almost solely for water-soluble drugs, such as nitroglycerine and morphine sulfate. The efficacy of the route was shown experimentally when Meltzer (1) in 1899 gave strychnine orally to dogs having the esophagus tied just above the cardia. In two hours, the animals were dead from strychnine poisoning. Karmel (2), in 1873, had likewise studied the absorption of drugs through the oral mucosa. In 1923, Mendel (3) demonstrated in patients the rapid absorption of nitroglycerine, morphine and other drugs when given in tablets placed under the tongue. Interest in the intraoral route of administration was renewed when Anderson, Haymaker and Henderson (4) reported in 1940 that desoxycorticosterone acetate (DCA) when given sublingually in solution was an effective treatment of adrenal insufficiency. Their observations were confirmed by Turnoff and Rowntree (5) and by Thaddea (6). Other reports showed the effectiveness of estrogens and of androgens in patients receiving sublingual solutions (7–11).

From 1940 to 1946, the use of DCA dissolved in propylene glycol and alcohol and administered in drops under the tongue was the method of choice in the treatment of Addison's disease at the University of California Hospital (12). During this period 30 patients with Addison's disease were supplied with this material through the clinic; more than two-thirds of these patients were under clinic care. The patients were given no supplementary salt, and no other preparation of DCA or adrenal cortical extract, except during acute illness. Among the 9 patients under the care of outside physicians there were 4 deaths. Four of our clinic patients were lost sight

Received for publication April 28, 1949.

* Present address: Experimental Biology and Medicine Institute, National Institutes of Health, Bethesda, Maryland.

of, and 1 died in the University Hospital due to an acute infection following the extraction of teeth. The patients for the most part carried on light occupations. The average daily dose of DCA by the sublingual route was 4.5 milligrams. The dosage ranged from 2 to 8 milligrams.

There were several advantages in sublingual administration over intramuscular injections or pellet implantation of the hormone: 1) the daily dose of hormone could be easily controlled, 2) every patient could administer the hormone to himself, 3) there was no need of sterile technique such as is required by intramuscular injection or pellet implantation, and 4) overdosage of DCA, which often occurred when the patient was first started on sublingual treatment, could be quickly controlled. There were, however, some drawbacks to the administration of a solution of DCA. Some patients objected to the taste of the propylene glycol and alcohol; and furthermore, meticulous care had to be used in the handling and the administration of the solution; otherwise the effectiveness of the therapy was lost. When the solution is cooled to 10° C. or below, the DCA is likely to crystallize out. When propylene glycol and absolute alcohol are exposed to the air, being hygroscopic, they readily absorb water sufficient to cause the DCA to precipitate from solution; and the undissolved DCA is very poorly absorbed. These disadvantages have been sufficient to discourage many clinicians from using the sublingual solution of DCA. At the present time these difficulties appear to be overcome by employing as the solvent a polyethylene glycol wax, a polymer which is a solid at body temperature, so that the DCA can be used in tablet form. The manufacture of these tablets was first worked out in the College of Pharmacy at the University of California (13). The DCA was dissolved in the melted wax and the material was then cooled and made into tablets, each containing 2.0 mg. of hormone.

CASE REPORTS

A group of 14 patients with Addison's disease has been treated with the intraoral tablets of DCA for periods of one and a half to two years. Except for 1 patient who was treated at the Station Hospital at Fort Belvoir, Virginia, the entire group has been followed at the University of California Hospital (UCH). Some of these patients had been maintained on sublingual DCA for five to seven years previously. Owing to the limitations of space, some typical histories will be summarized in detail, and only brief reference can be made to the remainder.

Case 1 (*U-12063, H. E. L.*). A single white man, aged 40 years, who was a ship's officer and draftsman, first noticed symptoms of adrenal insufficiency in July, 1936. He entered UCH April 19, 1937, complaining of weakness, nausea and vomiting. Positive clinical and laboratory data included dark brown pigmentation of the face and arms, blood pressure 98/75 mm.Hg, a glucose tolerance curve which did not rise over 100 mg.

per cent, plasma chloride 599 mg. per cent (as NaCl), blood NPN 33.7 mg. per cent, and a basal metabolic rate (BMR) of minus 14 per cent. A crisis was brought on by low salt intake in the hospital. Marked improvement followed the use of adrenal cortical extract supplemented by a high sodium and low potassium intake. High sodium intake was maintained and injections of adrenal cortical extract were given occasionally to bolster his waning energy. Testosterone propionate (Oreton), 25 mg. intramuscularly daily, was administered for two months and seemed beneficial, but the patient remained a semi-invalid. *1938:* Tablets of adrenal cortical hormone (Cortinsorbate) were given by mouth, one tablet 3 times daily, and salt intake remained high. He was hospitalized on two occasions, for five and seventeen days respectively, because of upper respiratory infections (Streptococcus viridans), and was treated with adrenal cortical extract and intravenous glucose and saline. *1939:* Desoxycorticosterone acetate (DCA) therapy, 2.5–5.0 mg. intramuscularly daily, was begun in June. Good health was regained to such a degree that he navigated a yacht in the San Francisco-Honolulu race. He became regularly employed as a draftsman. *1940:* DCA, 2.5 mg. intramuscularly, was being given daily, and was being supplemented by high salt intake. On May 29, he was hospitalized because of acute appendicitis; the operation was well tolerated and the postoperative course was uneventful. On August 1, the sublingual administration of DCA in propylene glycol-alcohol solution was commenced, 4 drops being given 6 times daily (6 mg.). As a result the patient's general condition improved, he gained in weight, and worked a 48-hour week without sick leave the entire year. *1941–46:* Under the care of a physician in another city, he was given DCA by the sublingual route 5–6 mg. daily, and methyltestosterone, 10 mg. daily. His general condition was satisfactory and he carried on his usual occupation until October, 1946, when acute pleurisy developed. Roentgenograms disclosed bilateral apical pulmonary tuberculosis, for which he was sent to a sanatorium. The intraoral use of tablets of DCA, 2 mg. twice daily, was started in November, 1946. *1947:* Intraoral use of tablets of DCA, 2 mg. twice daily, was continued; the tuberculosis subsided steadily. *1948:* He was discharged from the sanatorium in January; his maintenance dose of DCA was 2 mg. 3 times daily; methyltestosterone was continued. He was able to return to his work on a part-time arrangement.

Case 2 (*U-62220, D. M. W.*). A 74-year-old married white man, who was a timekeeper entered UCH in August, 1940, complaining of extreme weakness, dyspnea, anorexia, nausea, vomiting, abdominal and muscle pains, of two weeks' duration; he had lost 13 pounds in weight. Examination disclosed pigmentation of the skin on exposed surfaces of the body, a weak thready pulse, systolic blood pressure 100 mm.Hg (diastolic not ascertained), blood NPN 57 mg. per cent, blood sugar 88 mg. per cent, serum sodium 115 mEq./liter, and serum potassium 7.0 mEq./liter. Marked improvement ensued on DCA therapy, the maintenance dose being 5 mg. intramuscularly. On September 9, the use of DCA sublingually, 4 drops 6 times a day (6 mg.), was begun. *1941:* He was working forty-eight hours a week as timekeeper; the daily maintenance dose of DCA sublingually was 6 mg.; B. P. averaged 120/80 mm.Hg. *1942:* No change occurred in DCA dosage and the patient was working full time. He was in the hospital from January 19 to February 2 for study of the genito-urinary system; biopsy of the prostate showed no evidence of cancer. His serum sodium was 130 mEq./liter, and serum potassium, 5.1 mEq./liter. From November 24 to 30 he received an injection of adrenal cortical extract daily to restore his strength after a transcontinental trip. *1943–44:* The maintenance sublingual dose of DCA was 6 mg.; he also took methyltestosterone tablets sublingually, 10 mg. daily. *1945:* He was hospitalized from January 26 to February 6 because of pneumonia

and urinary tract infection. On admission he was stuporous and cyanotic; his temperature was 39° C, pulse rate 102 and respirations 30. He was treated with penicillin, adrenal cortical extract, and intravenous glucose and saline. He returned to work on March 15. The maintenance dose of DCA sublingually was 6 mg. *1946:* He continued to receive the same dose of DCA except for ten days when, because of tooth extraction, he was given DCA intramuscularly. *1947:* On February 20 the sublingual use of DCA by the drop method was discontinued in favor of 2.0 mg. tablets, given intraorally 3 to 4 times a day. During brief hospitalization for an upper respiratory infection, DCA was given intraorally in tablet form, 2 mg. 3 times a day, and was the only hormone therapy employed. *1948:* He was hospitalized because of active pulmonary tuberculosis. The maintenance dose of DCA has been 2 mg. 4 times daily.

Case 3 (*U-93802, H. A. H.*). A white woman, aged 31, who was a stenographer, entered UCH March 23, 1943, complaining of anorexia, nausea, vomiting, and weakness. Five weeks previously she had had similar symptoms and was treated in a hospital with glucose-saline intravenously and adrenal cortical extract intramuscularly. Past illnesses included exophthalmic goiter, for which thyroidectomy was done at the age of 15, and rheumatic heart disease occurring at the age of 21.

On entrance to UCH she had the following symptoms of adrenal insufficiency: weakness, tiredness, loss of weight, anorexia, nausea and vomiting, amenorrhea, pigmentation of the skin and mucous membranes, and a blood pressure of 95/65. At first her symptoms were kept under control by the sublingual use of DCA, 4 drops 5 times a day (5 mg.), and later 4 drops 4 times a day (4 mg.). In June a severe attack of urticaria developed; she was unable to eat or take sublingual therapy, and as a result entered UCH in an impending crisis. *1944–46:* Under the care of a private physician she received DCA sublingually, 4 drops 3 times daily (3 mg.); also desiccated thyroid up to 4 grains daily; she felt well and did full-time office work. *1947:* The intraoral use of DCA tablets, 2 mg. 3 times daily, was begun on June 19; the dose was reduced to 2 mg. twice daily in October. Her general condition remained satisfactory. *1948:* DCA tablets were continued in a dose of 2 mg. twice daily and thyroid in a dose of 5 grains daily. Her general condition was satisfactory.

Case 4 (*U-106701, F. M. F.*). A white man, aged 55, a laborer, entered UCH November 16, 1944, complaining of pigmentation of the skin, weakness and tiredness, dyspnea, nausea, vomiting, anorexia, and a weight loss of 70 pounds. The symptoms had first become evident about six months previously. Examination disclosed heavy pigmentation over the entire body and in the buccal mucous membrane; the blood pressure was 85/65 mm. Hg. At first he was given adrenal cortical extract in saline intravenously, after which he received it intramuscularly together with DCA in oil (also intramuscularly), 8 mg. daily. On discharge from UCH November 24 the dose of DCA, given by the sublingual route, was 4 drops 8 times a day (8 mg.); one month later this dose was reduced to 4 drops 5 times a day (5 mg.). *1945:* His condition was kept well under control by 5 mg. DCA daily, given sublingually. *1946:* The maintenance dose of DCA sublingually was 4 mg. *1947:* On March 20 the intraoral use of DCA in tablet form was begun, 2 mg. being given twice daily. His condition was satisfactory. *1948:* The maintenance dose was 2 mg. twice daily and he continued to feel well.

Case 5 (*U-132769, H. C. L.*). A white married housewife, aged 45, entered the hospital September 17, 1946, for treatment of Addison's disease. The onset of adrenal insuffi-

ciency had occurred three years previously; it was characterized by attacks of nausea and vomiting, weakness, and muscle pains. Her skin showed the characteristic pigmentation and she had lost 40 pounds in weight. Examination disclosed a blood pressure of 98/66, serum sodium 137 mEq./liter, serum potassium 3.4 mEq./liter, and urinary 17-ketosteroids 4.5 mg./24 hrs. Marked improvement followed the use of glucose-saline intravenously, adrenal cortical extract intramuscularly, and DCA sublingually. After leaving the hospital, she took DCA sublingually, 9–12 drops (2–3 mg.) per day and 8–12 grams of sodium chloride. *1947:* DCA therapy in tablet form used intraorally was begun March 1, the dose being 2 mg. 3 times daily. The sodium chloride was discontinued. The adrenal insufficiency has been satisfactorily controlled; on March 26 the serum sodium was 142 mEq./liter and the blood pressure 115/75 mm.Hg. *1948:* Because of domestic trouble, she suffered a severe nervous upset which caused her to stop the DCA and to neglect her diet. This precipitated a severe adrenal insufficiency which necessitated hospitalization and treatment with adrenal cortical extract. Except for this episode the patient has continued to be well maintained on 2 mg. of DCA twice daily and small amount of methyltestosterone.

Case 6 (*U-134166, A. C. P.*). A 55-year-old white man, a ferryboat tender, entered UCH October 28, 1946, complaining of marked fatigability, weakness, loss of libido, nausea, vomiting, alternating diarrhea and constipation, darkening of the skin, dyspnea on exertion, and weight loss. Examination disclosed generalized pigmentation, blood pressure 90/30 mm.Hg, serum sodium 137 mEq./liter, serum potassium 4.5 mEq./liter, urinary 17-ketosteroids (ketonic fraction) 6.0 mg./24 hrs., and delayed excretion of administered water as brought out by the Kepler-Power test. Therapy consisted of DCA by the sublingual route only. He was discharged from the hospital November 11; the maintenance dose of DCA sublingually was 3 mg. daily. *1947:* He received 3 mg. DCA sublingually daily (4 drops 3 times a day), and took additional salt as desired. He continued working as ferryboat tender, felt well, had gained weight, and had return of sexual function. On November 6, the intraoral use of DCA tablets, 2 mg. twice daily, was begun. *1948*: During an uneventful course he was well maintained on 2 mg. twice daily.

Case 7 (*U-124076, F. T. L.* Station Hospital, Ft. Belvoir, Va.). A married white man, aged 59, who was an engineer, was admitted to hospital on June 27, 1947, because of a convulsive seizure. During the previous twenty-four hours he had had abdominal cramps, diarrhea, and headache. For the preceding two months he had complained of marked fatigability, anorexia, and abdominal discomfort. Examination disclosed dark brown pigmentation of the face, neck, arms, and hands, purple pigmentation of the lip and gum margins, blood pressure 96/66 mm.Hg, rectal temperature 97° F., serum sodium 131 mEq./liter, and serum potassium 7.6 mEq./liter. Roentgenograms showed calcified nodules in the right lung, but none in the region of the adrenal glands. Initial treatment consisted of 5 mg. of DCA, 5 cc. of adrenal cortical extract, and 8 Gm. of sodium chloride daily. After ten days on this regimen edema was apparent, whereupon the hormone therapy was reduced to 3 mg. DCA daily. Steady improvement ensued, and one month later the intraoral use of DCA tablets was begun, 2 mg. being given twice daily. After another six weeks the dose was decreased to 2 mg. once daily.

Three months after treatment was initiated the blood pressure was 125/88, serum sodium 146 mEq./liter, serum potassium 6.4 mEq./liter, total serum proteins and A/G ratio within normal range, urinary 17-ketosteroids 5.9 mg./24 hrs., BMR minus 13 per cent, and blood count normal. At the present time the patient receives 2 mg. of DCA

daily intraorally; his blood pressure is 122/80, and he works full time as a consulting engineer.

Case 8 (*U-96568, J. O. P.*). A single white butcher, aged 38, had recognized Addison's disease since 1941. Beside the usual symptoms and signs, he had thoracic spondylitis and collapse of vertebrae (tuberculous), and a nonfunctioning right kidney. He was maintained with sublingual DCA, 4 mg. daily, from 1943 to 1947, when intraoral tablets, 2 mg. twice daily, were begun. He had progressed from bed rest to graduated activity (1944) to full-time occupation as watchmaker (1945–), and is still maintained in good condition.

Case 9 (*U-98750, B. C. R.*). A white housewife, aged 55, had Addison's disease (1943), rheumatic heart disease, and the menopausal syndrome. She was maintained by a daily dose of 4 mg., later 6 mg., of DCA sublingually to 1947, and then was given 4 mg. daily intraorally. When she was given 6 mg. daily, edema developed. Except for lobar pneumonia in 1948, with full recovery aided by penicillin and adrenal cortical extract, she was well maintained throughout with 4 mg. intraorally.

Case 10 (*U-142768, M. F. McN.*). A white housewife, aged 41, with Addison's disease (1945) was controlled for the first one and one-half years by 1 cc. of cortical extract (Upjohn) and 8 Gm. of sodium chloride daily. She was then maintained by 2 mg. DCA intraorally 3 times daily, reduced after four months to 2 mg. twice daily. This dosage had kept her in good condition for over one year thus far.

Case 11 (*U-107041, R. W. M.*). A marine electrician, aged 46, was treated for one year for Addison's disease by means of 5 cc. cortical extract intramuscularly 3 times a week. Sublingual DCA, 5 mg. daily, maintained him while he worked full time in a shipyard for two years; during this time he underwent appendectomy without trouble. Intraoral DCA was started in early 1947, using 2 mg. 4 times daily and later 2 mg. 3 times daily, together with 10 mg. of methyltestosterone daily. He is now satisfactorily maintained by 2 mg. twice daily.

Case 12 (*U-112895, H. H.*). A housewife, aged 52, had an eight months' history of Addisonian symptoms, and presented pyelonephritis due to *E. coli*. After the infection had been cleared, she was maintained uneventfully with sublingual DCA, 5 mg. daily, except for exacerbations of pyelonephritis. Intraoral DCA was started early in 1947, 2 mg. 4 times daily at first, and later only 2 mg. twice daily; she has since been well controlled on this dosage, although recrudescences of infection have occurred.

Case 13 (*U-118581, F. D.*). A white housewife, aged 45, was treated for two years for Addison's disease by means of salt, adrenal extract orally, and weekly injections of extract. The Wilder test on admission precipitated a crisis. Sublingual DCA, 6 mg. daily, was begun but was reduced to 3 mg. daily on which dose she was well maintained until 1947, when intraoral DCA tablets were given, 4 mg. daily. She felt well and was able to do her work. Dosage was recently increased to 6 mg.; she continues to feel well.

Case 14 (*U-144448, S. T. B.*). A white high school boy of 18 years, with well-marked Addison's disease, was managed successfully with 5 mg. DCA daily by intramuscular injection. Intraoral tablets, 2 mg. twice daily, then served for maintenance, except during two weeks' hospitalization for a severe febrile illness, when cortical extract was also given by injection. He has been well maintained with intraoral dosage only.

DISCUSSION

In this group of 14 patients with Addison's disease there were 8 men and 6 women. The ages ranged from 18 to 73 years, although all but 4 were past 40 years of age. The duration of the disease varied from one to twelve years. Ten of the patients had been treated previously with sublingual DCA; in the case of 2 patients, this method of therapy had been used as long as seven years. The entire group of patients has been on the intraoral tablets for from eighteen months to two years.

All of these patients continued with light occupations; 2 of the patients, however, had their work interrupted by hospitalization for tuberculosis. On the whole, considering the well-known susceptibilities of people with adrenal insufficiency, they all withstood the ordinary vicissitudes of life with surprisingly good stamina.

There was no evidence of toxicity from the absorption of the polyethylene glycol wax which was used as the vehicle for the DCA. The pharmacologic properties and toxicity of this substance have been extensively studied regarding oral administration (14, 15) parenteral (intraperitoneal and intravenous) administration in animals (14) and in man (15) and percutaneous administration (16, 17, 18). The intravenous injection of 20 cc. of physiologic saline containing 1 Gm. of polyethylene glycol wax in 6 normal human subjects was attended by no symptoms. Of the total injected dose, 96.25 per cent was recovered from the urine within a 12-hour period (15). On oral administration of 10 Gm. to 6 normal human adults there was no untoward reaction and practically none of the material was absorbed from the gastro-intestinal tract.

In the clinical series reported herein the amount of polyethylene glycol wax used in each tablet of DCA was 0.2 Gm., or a total average intake of 0.45 Gm. daily. The toxicity of the vehicle is so low as to merit no consideration under these conditions of use.

The average daily requirement of DCA when administered by the intraoral tablet was 4.5 mg. Ten of the patients were well controlled on 4 mg. One patient required only 2 mg. The 2 patients with pulmonary tuberculosis required 6 mg. and 8 mg. respectively while the infection was active. In no case was supplementary salt given. It was found that the patients who had been previously treated with sublingual DCA required substantially the same amounts of DCA when given the hormone by intraoral tablets.

The efficacy of the intraoral method of administration of DCA compares favorably with that of the intramuscular method. The average maintenance dose in this series of patients who had received no supplementary salt was 4.5 mg., whether given by sublingual solution or by intraoral tablets. Thorn, Dorrance and Day (19) have reported on a series of 141

patients with Addison's disease in which the average maintenance dose of DCA by the intramuscular route was 3.8 mg., when 3 to 4 Gm. of supplementary salt was given. It is difficult to explain the low efficiency of the sublingual method which Wilson (20) and Thorn *et al.* (21) have reported, unless we assume that their patients failed to carry out with meticulous care the instructions for sublingual administration, or that the vehicle which they used did not afford equally efficient absorption of the steroid.

SUMMARY

Fourteen patients with Addison's disease have been well maintained by the intraoral administration of desoxycorticosterone acetate (DCA) in tablet form for periods of eighteen months to two years. The average daily requirement of DCA was 4.5 milligrams. There was no evidence of toxicity from the use of the polyethylene glycol wax which was used as the vehicle for the hormone.

REFERENCES

1. Meltzer, S. J.: An experimental study of the absorption of strychnine in the different sections of the alimentary canal of dogs, *Am. J. M. Sc.* **118**: 560–570 (Nov.) 1899.
2. Karmel, I.: Über die Resorption in der Mundhöhle, Med. Diss. Dorpat, 1873, cited by Miescher, K., and Gasche, P.: *Schweiz med. Wchnschr.* **10**: 279–281 (Mar. 7) 1942.
3. Mendel, F.: Die perlinguale Applikation der Medikamente, *München med. Wchnschr.* **70**: 1526, 1923.
4. Anderson, E.; Haymaker, W., and Henderson, E.: Successful sublingual therapy in Addison's disease, *J.A.M.A.* **115**: 2167–2168 (Dec. 21) 1940.
5. Turnoff, D., and Rowntree, L. G.: Successful sublingual therapy in Addison's disease, *J.A.M.A.* **116**: 2016 (May 3) 1941.
6. Thaddea, S.: Über wirksame sublinguale Nebennierenrindenhormontherapie des Morbus Addison, *Klin. Wchnschr.* **20**: 1237–1239 (Dec. 13) 1941.
7. Salmon, U. J., and Geist, S. H.: Buccal absorption of α-estradiol in propylene glycol, *Proc. Soc. Exper. & Med.* **45**: 766–769 (Dec.) 1940.
8. Hall, G. J.: Clinical experiences with the sublingual administration of alpha estradiol, *J. Clin. Endocrinol.* **2**: 26–28 (Jan.) 1942.
9. Lisser, H.; Escamilla, R. F., and Curtis, L. E.: Testosterone therapy of male eunuchoids, *J. Clin. Endocrinol.* **2**: 351–360 (June) 1942.
10. Castrodale, D.; Loeffel, E., and MacBryde, C. M.: Sublingual administration diethylstilbestrol; comparison of routes in therapy, *J. Clin. Endocrinol.* **2**: 569–570 (Sept.) 1942.
11. Hurxthal, L. M.: Sublingual use of testosterone in 7 cases of hypogonadism; report of 3 congenital eunuchoids occurring in one family, *J. Clin. Endocrinol.* **3**: 551–556 (Oct.) 1943.
12. Anderson, E., and Haymaker, W.: The technic of sublingual administration of desoxycorticosterone acetate in the treatment of Addison's disease, *Clinics* **1**: 475–479 (Aug.) 1942.
13. Anderson, E.; Kinsell, L.; Daniels, T. C., and Henderson, E.: The intraoral

administration of desoxycorticosterone acetate tablets in the treatment of Addison's disease, *J. Clin. Endocrinol.* **8**: 884–886 (Oct.) 1948.

14. Smyth, H. F., Jr.; Carpenter, C. P., and Shaffer, C. B.: The toxicity of high molecular weight polyethylene glycols; chronic oral and parenteral administration, *J. Am. Pharm. A.* **36**: 157–160, 1947.
15. Shaffer, C. B., and Critchfield, F. H.: The absorption and excretion of the solid polyethylene glycols ("Carbowax" compounds), *J. Am. Pharm. A.* **36**: 152–157, 1947.
16. Clark, W. G.: Studies on the penetration of sulfonamides into the skin. III. Penetration of sulfanilamide and sulfathiazole into intact and injured skin of guinea pigs from various vehicles, including polyethylene glycols ("Carbowax"), *Am. J. M. Sc.* **212**: 523–534 (Nov.) 1946.
17. Maynard, M. T. R.: Polythylene glycol vehicles in dermatology, *J. Invest. Dermat.* **8**: 223–225 (Apr.) 1947.
18. Luduena, F. P.; Fellows, J. K.; Laqueur, G. L., and Driver, R. L.: Toxicity of polyethylene glycols by repeated epidermal applications, *J. Indust. Hyg. & Toxicol.* **29**: 390–392 (Nov.) 1947.
19. Thorn, G. W.; Dorrance, S. S., and Day, E.: Addison's disease: evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients, *Ann. Int. Med.* **16**: 1053–1096 (June) 1942.
20. Wilson, A.: Sublingual therapy in Addison's disease, *Lancet* **1**: 762–763 (June 27) 1942.
21. Thorn, G. W.; Greif, R. L.; Coutinho, S. O., and Eisenberg, H.: Relative effectiveness of several methods of administering desoxycorticosterone acetate, *J. Clin. Endocrinol.* **1**: 967–976 (Dec.) 1941.

A CASE OF RUDIMENTARY TESTES, DELAYED GROWTH AND CONGENITAL MALFORMATIONS

TURNER'S SYNDROME IN A MALE

J. REFORZO-MEMBRIVES, M.D., A. TRABUCCO, M.D. AND F. ESCARDÓ, M.D.

Instituto de Semiologia, Buenos Aires, Argentina*

THE following is a case presenting in a male patient the same characteristics described in 1938 by Turner (1) in females.

CASE REPORT

A.C.F., an Argentinian boy, 10 years and 3 months old, came to the Institute in November 1946.

History and presenting illness. He was the second of three sons in a family which was otherwise normal except for the fact that the father contracted syphilis. He received treatment which he could not identify. The mother's pregnancy and delivery were normal, and the infant's birth weight[1] was 5.5 Kg. The child was given Sulpharsenol injections for three years. His head was unusually large but did not increase in size after the third year, according to the mother. The only other abnormality noticed during the first years was the delayed growth. He walked and talked at 11 months and had normal bowel movements. Very marked cutaneous folds on both sides of the neck and surrounding the eyes were present since birth, as well as abundant warts and moles. The retarded growth persisted. In other aspects the child was normal; he went to school at the age of 8 and progressed well. He had measles at 2 years of age, whooping cough at 4, and had his tonsils and adenoids removed at the age of 7. He has always been "fatty and large headed."

Physical examination. His height was 112 cm. and weight 25 Kg. (Normal height and weight for this age, 135 cm. and 32.7 Kg., according to the tables of Winocour P. (2).) He had a large abdomen and smooth skin. There were abundant small nevi on the forehead and nose and many warty nevi, from the size of a pinhead to that of a lentil, on the neck and thorax, especially on the back and extremities (Fig. 1). In the crural aspect of the right thigh there was an elongated nevus measuring 7×9 mm. His scalp was thin, showed diffuse alopecia in the occipital region. On the neck, the hair reached to the fifth spinous cervical apophysis (Fig. 2). *Osseous development.* He showed dorsal kyphoscoliosis, an accentuated cubitus valgus, slight genum valgum and a large head with marked frontal protuberances (Fig. 3). His eyebrows were very sparse and there was a deep horizontal scar on the forehead caused by a fall at the age of 2. Depression of the cheek bones gave the impression of exophthalmos. *Exophthalmometric values* (Luedde): right eye, 20 mm.; left eye, 20 mm. There was bilateral epicantus. Ocular movements were preserved. The sclerae were bluish and the pupils were round and slightly eccentric. The photo-

Received for publication May 31, 1949.

* Director—Prof. T. Padilla.

[1] According to the mother's statement.

FIG. 1. A.C.F.—Age 10 years and 6 months. Webbed neck, cubitus valgus and abundant nevi.

FIG. 2. A.C.F.—Mastoid acromial folds and diffuse alopecia in the occipital area.

motor reflex was normal. *Eye* tests and ocular fundus examination by Dr. Magin Diez showed normal pupillary reaction to accommodation and convergence. *Nose:* there was a depression of the bridge. *The mouth* showed an ogival palate. He had a webbed *neck* (Sphinx neck) (Figs. 1, 2 and 3) with cutaneous folds extending from the mastoid towards the acromioclavicular joint, more marked on the right side. The *thyroid* could not be palpated. The *thorax* was deformed by kyphoscoliosis. The *respiratory tract* was normal. *Circulatory system:* On palpation the apex of the heart was in the fourth space, at

FIG. 3. A.C.F.—Webbing of the neck. Bilateral epicanthus.

6 cm. from the median line. The cardiac sounds were normal except for a systolic murmur at the apex. The pulse was small and regular with a rate of 87. Arterial pressure (auscultatory method) was 114/68 mm. of Hg. The *abdomen* was protuberant with hypotonic walls and there was no pain on superficial and deep palpation. *Liver* percussion showed that the upper border edge of the liver was of normal contour within the fourth intercostal space. *The spleen and kidneys* could not be palpated. *Genitals:* The patient had a small, well-shaped penis, with a marked balanopreputial fold; the urethral meatus was not hypospadic. The scrotum was small with few folds. The testes were small (right, 16×8 mm. and left, 15×7 mm.) correctly placed in the scrotum, perfectly mobile, and normal in contour, consistency and sensitivity. The prostate was hypoplastic and on palpation it was possible to feel only a small amount of soft, well-outlined tissue the size of a chick-pea, protruding slightly into the rectum. *Nervous system.* There was a peculiar distribution of the muscle tonus in the static planus (flatfoot; marked hypotony of the whole abdominal wall and slight hypertony of the sural gluteus and quadriceps muscles). The *mental level* determined by Dr. Serebrinsky (Terman test) revealed that when the patient was 10 years and 9 months old, his mental age was that of a boy aged 9 years and 8 months, with an intellectual quotient of 0.90. His rating was normal-obtuse close to subnormal, and his failures were especially associated with the memory tests.

Laboratory tests. The Wassermann and presumptive Kahn tests on blood gave negative results in the patient and in his mother. The red blood cell count was 4,600,000, white cell count 7,500, hemoglobin 95 per cent (14.6 grams per 100 cc.), color index 1.03, and the differential count showed neutrophiles 67, lymphocytes 28, acidophiles 2 and monocytes 3. The blood sugar was 87 mg. per 100 cc. and a glucose tolerance curve with 1 gram of glucose per kilogram of ideal theoretical weight showed: fasting—91 mg. per 100 cc.; at 30 minutes—111 mg.; and at 75 minutes—65 mg. An insulin tolerance curve, according to the technique of Fraser and associates (3) with 0.1 U. of insulin per kilogram of theoretical ideal weight (2.1 U.) intravenously injected gave the following results: fasting, 90 mg. per 100 cc. of blood; at 20 minutes, 47 mg.; at 30 mintues, 66 mg.; at 60 minutes, 79 mg.; and at 90 minutes, 83 mg. Blood urea was 30 mg. per 100 cc. and

FIG. 4. A.C.F.—Lateral roentgenogram of the skull.

cholesterol 150 mg. per 100 cc. Plasma sodium was 334 mg. per 100 cc. of plasma (145 mEq. per liter), and chlorides 369 mg. per 100 cc. (104 mEq. per liter). Serum calcium was 11 mg. per 100 cc. and inorganic phosphorus 2.2 mg. per 100 cc. Alkaline phosphatase in serum was 4.6 Bodansky units. The urine was normal. *Basal metabolic* rates were -2 and ± 0 per cent. An *electroencephalogram* (performed by Dr. Mosovich) showed a medium voltage curve with predominant slow frequencies, from 5 to 7 cycles per second and even less, irregularly distributed in all the explored areas; the parieto-occipital alpha rhythm was irregular, with rapid superimposed frequencies. There were no focal signs. Before the hyperventilation, some hypersynchronisms could be observed (increase of the extent without modification of the rhythm) and disrhythmical discharges (modifications in the frequency) simultaneously registered in all the electrodes. The hyperventilation produced a slight decrease of the frequency with increase of the irregularities and moderate increase of the disrhythmical discharges. In summary, the electroencephalogram revealed a bioelectrical activity of decreased metabolism, without focal signs (slight unsteadiness of the bioelectrical rhythm and predominance of slow frequencies). The *electrocardiogram* showed a sinus rhythm, normal auriculoventricular conduction and deviation of the electrical axis towards the right; in short, it did not reveal any cardiac

disturbances. *Roentgenograms* showed a normal cardiovascular image without aortic coarctation. The x-ray examination of the skull (Fig. 4) showed no evidence of cranial hypertension; the sella turcica was normal in shape and size but there was a disparity between the development of the bones of the face and that of the cranial vault, similar to that observed in Crouzon's disease. There was no alteration in the number or fusion of the vertebrae of the cervical spine (Fig. 5), the Klippel Feil's syndrome being thus excluded. The dorsal spine showed marked decrease in the intensity of the shadows (Figs. 6 and 7). Signs of osteoporosis were also evident in the iliac bones (Fig. 8). The x-ray study of the long bones showed delayed closure of the epiphyses. The osseous development, according to the Atlas of Todd (4) corresponded to that of a boy 5 years and 8 months old (age of the patient, 10 years and 3 months). *Hormonal tests:* 17-ketosteroids, determined by Dr. O. Repetto (5) in 24-hour urine showed on January 31, 1947, 0.6 mg.; less than 0.5 mg. on February 3; 1.2 mg. on March 18, 1947 (age of patient 10 years and 6 months); and 3 mg. November 1, 1948 (age 12 years and 2 months). According to Talbot and associates (6) the normal daily rate is 1.9 mg. at 10 years and 2.6 mg. at 11 years. The values found by Raices and Rivara (7) in Buenos Aires, are slightly different. According to them, the rate of 17-ketosteroid excretion of our patient seems slightly decreased. The determination in the urine of the follicle-stimulating hormone of the hypophysis, investigated under the direction of Dr. F. de la Balze following the technique of Klinefelter and associates (8) gave the following results: negative for 48 mouse units (October 22, 1947); negative for 96 mouse units (October 27, 1947) (age of the patient 11 years 2 months); negative for 24 mouse units (March 17, 1948) (age 11 years 6 months); negative for 12 and 6 mouse units (May 5, 1948) (age 11 years and 8 months); and negative for 6 mouse units (October 15, 1948) (age 12 years and 2 months).[2] The data available (6) indicate that gonadotropins are not detectable in the urine of normal boys before the age of 12.

FIG. 5. A.C.F.—Cervical spine.

Biopsy of the testis. A small portion of tissue the size of a grain of corn was removed. Macroscopically this specimen showed shiny yellowish-white tissue which constituted a

[2] A further test for urinary gonadotropins, performed with the same technique, gave negative results for 6 mouse units on September 1, 1949, when the boy was 13 years old.

FIG. 6. A.C.F.—Dorsal spine, front.

FIG. 7. A.C.F.—Dorsal spine, lateral. Decreased intensity of the vertebral shadows.

rather compact mass, very different from the structure of the normal testis in which the tissue is yellow, opaque and easily separable into long, narrow tubules. The usual histologic technic was employed. With hematoxylin and eosin stain and Masson's trichrome method, under low magnification (Fig. 9, A and B) a striking disproportion between the intertubular tissue and the seminiferous tubules was evident; the latter were small and grouped in very definite zones; these zones corresponded to the different segments in which the testis was divided, but they were much more strikingly demarcated. Under

FIG. 8. A.C.F.—Pelvis.

higher magnification (Fig. 9, C and D) the structural characteristics of these walls could be seen. They were formed by connective tissue of the vascular type, intimately mixed with the albuginea of the testis and of the same structure; this connective tissue contained vessels and nerves of different sizes giving the impression of a functioning zone. The testicular albuginea was thickened and consisted of connective tissue of the adult type containing very elongated cells with dark elongated nuclei and hyaline protoplasm. The seminiferous tubules showed very definite characteristics and were formed by a tubular wall lined with epithelium, usually with a well defined lumen which was occupied by a reticular substance containing cell debris undergoing kariokinesis and necrobiosis. The walls of the tubules were formed by a thin layer of compact elongated cells with elongated nuclei. This wall was thinner than normal and constituted the implantation base line of the intratubular epithelium. The intratubular epithelium was formed by two predominant types of cells: (a) The medium sized and capriciously shaped cells that

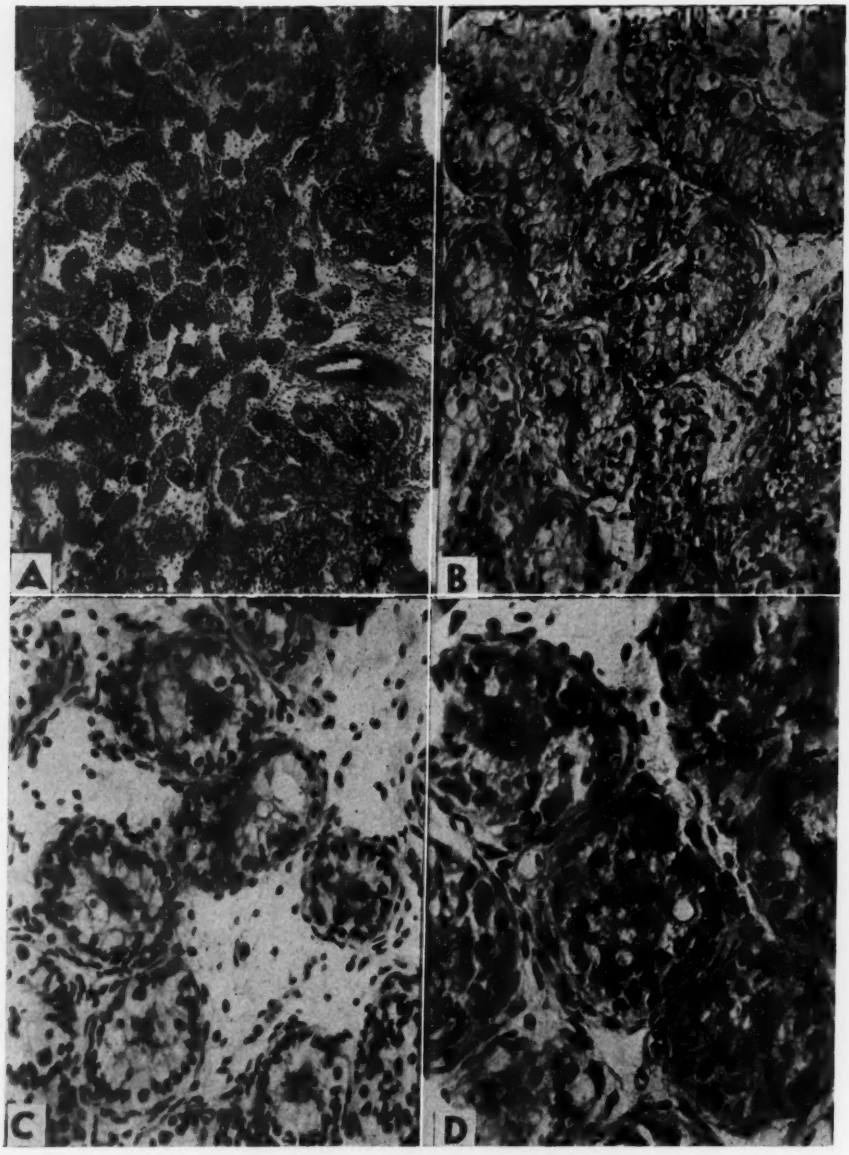


FIG. 9. A, B, C and D.—Biopsy specimen of testis of the patient A.C.F. with Turner's syndrome (description in the text).

were usually found against the tubular walls; their protoplasm was sometimes well outlined and sometimes diffuse without precise outline; it was spongy and reticulous and characteristically of acid-staining reaction. The nuclei were round, irregular, lightly stained and much larger than those of the other elements. Accordingly, these cells may be classified as Sertoli cells in activity. (b) Small, round shaped cells, very similar to lymphocytes though of larger size, that were formed by a well outlined protoplasm, with less marked acid-staining reaction than the Sertoli cells; their nuclei were round and occupied most of the cell; they were homogeneous and appeared strongly stained. These cells were found near the tubular wall, but not necessarily in contact with it. In some areas they even formed three layers, without particular order or symmetry. Most of

FIG. 10. *Specimen of testis of a normal child 10 years old,* showing seminiferous tubules with normal walls, and germinal epithelium with basal spermatogonia. In some tubules there are differentiated first degree spermatocytes. Sertoli cells are normal. Interstitial tissue is formed by normal connective elements. It is impossible to distinguish Leydig cells.

them had the same characteristics as the basal spermatogonia; few elements showed the signs of first degree spermatocytes. No further differentiated elements of the germinal epithelium were seen. The interstitial tissue between these tubules was essentially characterized by large free spaces without any kind of cellular elements; it was formed by connective tissue in different stages of development, suggesting the existence of edema in the fibrillar connective tissue. There was no evidence of Leydig interstitial cells. The rare cells that could be seen were difficult to distinguish. In summary, the histologic findings were very different from those of a biopsy specimen from the testes of a normal 10-year-old boy (Fig. 10).

Somatic evolution. At the age of 10 years and 8 months (five months after the first measurement) the patient's height was 113 cm., and his weight was 25 Kg. At 11 years and 8 months his height was 115.5 cm., pubis-floor distance 57 cm., pubis-vertex distance 58.5 cm., span 110 cm. and weight 26 Kg., an increase of 3.5 cm. in height in one year and five months. (For the age of the patient the ideal height would have been 141.5 cm. and the weight 37 Kg., according to the tables of Winocour (2).) At 12 years and 3 months his height was 117.5 cm., pubis-floor distance 58.5 cm., pubis-vertex distance 59 cm., span 112 cm. and weight 26.7 Kg. (The ideal height would have been 144.2 cm. and the weight, 39 Kg.) There was an increase of 5.5 cm. in height in the two years which had elapsed since the time of the first visit.

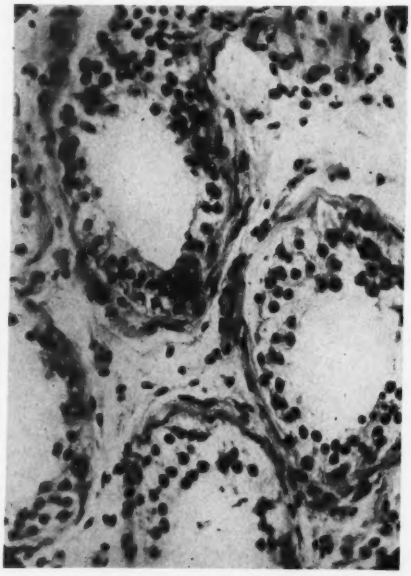


FIG. 11. *Specimen of testis of an hypophyseal dwarf 24 years old,* showing seminiferous tubules with normal walls, germinal epithelium with basal spermatogonia, and some primary spermatocytes. Complete absence of spermatids and spermatozoids, classified the condition as a second degree degeneration. Interstitial tissue is formed by lax connective tissue, with some Leydig cells.

DISCUSSION

In 1938 Turner (1) described, in females, a syndrome essentially characterized by delayed growth, retarded sexual development, webbing of the neck and cubitus valgus. Capurro in 1940 (9) studied a case of this syndrome. In 1942 Varney and associates (10) and Albright and coworkers (11) gave a great impetus to the study of clinical cases observed in females and essentially characterized, according to the authors, by ovarian insufficiency, increased pituitary gonadotropins and dwarfism. This syndrome

has since been studied by many different investigators: Schneider and McCullagh in 1943 (12), Wilkins and Fleischmann in 1944 (13), Del Castillo, de la Balze and Argonz in 1947 (14), and Dorf, Appelman and Liveson in 1947 (15). Of great help to these investigations have been the hormone determinations (pituitary gonadotropins, 17-ketosteroids and estrogens) which permitted an approach to the study of the different interrelations invaluable for the explanation of the physiopathology of this complex syndrome. Some of the mentioned investigators, particularly Albright and associates and Del Castillo and coworkers, believe that the clinical cases reported by Turner probably constitute a sub-group that ought to be included in the syndrome studied by them. This syndrome, however, has very vague boundary lines, since the authors are not in complete agreement as to the different features. They all agree on the existence of a marked ovarian insufficiency, but the other essential features of the clinical picture such as dwarfism, increased gonadotropins in the urine, and decreased 17-ketosteroid excretion, are not absolutely constant (Table 1). This lack of uniformity in the elements of the syndrome raises

TABLE 1. THE "SYNDROME OF THE RUDIMENTARY OVARIES" ACCORDING TO DIFFERENT AUTHORS

Authors	Ovaries	Height of patient	Gonadotropins in the urine	17-ketosteroids in the urine	Relation between ovarian insufficiency, increased gonadotropins and delayed growth
Varney and assoc. 1942 (10)	Insufficient. Aplasia not constant.	Short	High	Low androgens.	No satisfactory explanation. It can be genetic and not functional.
Albright and assoc. 1942 (11)	Insufficient.	Short	High	Low, but not minimum.	Probably hypocorticalism from lack of hypophyseal stimulation, due to the hypoestrogenism.
Wilkins and assoc. 1944 (13)	Insufficient.	Short, but not constantly.	High, but not constantly.	——	Genetic origin, rather than endocrine.
Goldberg and assoc. 1947 (16)	Absent.	Short	High	Lowest limit.	——
Del Castillo and assoc. 1947 (14)	Rudimentary.	Short, but not constantly.	High	Low, but they can be normal or high.	——
Lisser and assoc. 1947 (17)	Insufficient.	Short, but not constantly.	High	——	Genetic origin.
Dorff and assoc. 1947 (15)	Insufficient.	Short	Absent	Normal	Genetic origin.

the problem of its pathogenesis and weakens the opinion of Albright who believes that in the absence of the ovarian estrogens the production of the luteinizing hormone (or luteotropin) in the hypophysis decreases, thus diminishing the stimulus for the production of androgenic substances by the suprarenal cortex. This decrease, shown in the low values in urinary 17-ketosteroids, might be responsible for the defective growth. It is difficult to reconcile this theory with the existence of the syndrome of "rudimentary ovaries" in patients with normal and even increased 17-ketosteroid excretion (Del Castillo and associates). Most authors are inclined to believe that the association of rudimentary ovaries with defective growth is due to genetic factors; Dorff (15) believes that the severe alterations of the gonads as well as the slight alterations of the hypophysis are congenital and that the latter could be responsible for the delayed growth.

In the case here reported the same features of the clinical cases originally described by Turner in females, are evident in a male patient, namely, delay of growth, gonadal insufficiency, webbing of the neck and cubitus valgus. As far as we know, only 2 other cases of Turner's syndrome in males have been reported previously (18, 19). There also exists plain verrucous nevus, the association of which with other congenital malformations has been pointed out by Maranon (20). Among the features of the syndrome reported here we should like to stress especially the histologic studies of the testis, which show the doubtful existence of Leydig cells and the arrest of the evolution of the germinal epithelium at the stage of basal spermatogonia. On the other hand, the Sertoli cells not only are present but are well developed morphologically. As far as the hormonal studies are concerned, the urinary 17-ketosteroids seem slightly low and in accordance with the biopsy of the testis. Until now it has been impossible, in spite of repeated search, to find pituitary gonadotropins in the urine even in the smallest quantities that the methods available can determine. We must remember that Goldberg and associates (16) have found increased gonadotropins in a girl 12½ years old with ovarian agenesis. Del Castillo and associates have found increased urinary gonadotropins in patients from 10 to 13 years of age with the syndrome of rudimentary ovaries.

The biopsy of the testis in the present case is particularly interesting, especially in connection with the hormonal findings. From Albright's (21) and Del Castillo's (22) studies it can be deduced that the three fundamental elements which constitute the testis (germinal epithelium, Sertoli cells and interstitial cells) may be independently affected. Thus Klinefelter and associates (23) have found, in their clinical cases, hyalinization of the germinal epithelium and of the Sertoli cells with integrity of the Leydig interstitial cells, and at the same time an increase of follicle-

stimulating hormone in the urine. On the other hand, Del Castillo and associates have found, in their patients, absence of the germinal epithelium but normal Sertoli cells and intact Leydig interstitial cells; the follicle-stimulating hormone was not increased. The clinical case here reported presents, together with an apparent absence of the interstitial tissue, a poor development of the spermatic epithelium but Sertoli cells which seem to be active; at the same time not only are the gonadotropins not increased, but search for them in the urine has constantly yielded negative results.

It appears from the comparison of histologic testicular specimens, that when the Sertoli cells are intact, there may exist a deficiency of the germinal epithelium (Del Castillo) as well as a deficiency of the Leydig cells (present case) without increase of the follicle-stimulating hormone in the urine (Table 2). This correlation strengthens the opinion of Del Castillo

TABLE 2. THE TESTICULAR HISTOLOGY AND THE FOLLICLE-STIMULATING HORMONE IN THE URINE

Authors	Histology of testis	F.S.H. in urine
Klinefelter, Reifenstein and Albright, 1942 (23)	Germinal epithelium: Absent Sertoli cells: Absent Leydig cells: Preserved	Increased
Albright and assoc. 1941 (21) Heller, Nelson and Roth 1943 (24)	Germinal epithelium: Absent Sertoli cells: Absent Leydig cells: Absent	Increased
Del Castillo, Trabucco and de la Balze, 1947 (22)	Germinal epithelium: Absent *Sertoli cells: Preserved* Leydig cells: Preserved	*Not increased*
Present case	Germinal epithelium: retarded, not absent *Sertoli cells: Preserved* Leydig cells: Practically absent.	*Not increased*

and coworkers who are inclined to believe that Sertoli cells produce a substance comparable to estrogen, which can regulate the secretion of the follicle-stimulating hormone in the hypophysis. This substance can be considered homologous to the "inhibine" or "X hormone" which, according to Albright and associates, would be produced by the tubules.

The hypogonadism with delayed growth and congenital malformations, as it appears in the present patient, reminds us of the similar clinical case in females which has so greatly attracted attention since Turner's report. Thus this clinical case would be the homologue in the male of what Del

Castillo and coworkers (14) have called "syndrome of rudimentary ovaries" in the female. In our case, however, it has not been possible to prove the existence of hypophyseal gonadotropins in the urine, as was demonstrated in girls of the same age with rudimentary ovaries; therefore, it is impossible to attribute to hypofunction of the testis the same importance that is attributed to the ovaries in the pathogenesis of the syndrome. This is the reason why the differential diagnosis between our case and hypophyseal dwarfism is not so obvious. The differences are:

Morphologic: Hypophyseal dwarfs generally show a more marked delay in growth. They do not usually show the congenital malformations present in our patient, such as webbing of the neck, cubitus valgus and epicanthus.

Functional: The urinary 17-ketosteroids are not as low in our case as they are in the hypophyseal dwarf. The insulin tolerance curve in our case was within the range of normal, showing a response very different from the lack of reaction to hypoglycemia in hypophyseal dwarfs. In half of the clinical cases of "rudimentary ovaries" studied by Del Castillo and associates there was a slight decrease in the response to the insulin. The biopsy specimen of the testis, on the other hand, was very similar to that of a hypophyseal dwarf (Fig. 11) and very different from that of a normal child of about the same age (Fig. 10).

The foregoing arguments indicate that, in our case, there exists a series of congenital anomalies and perhaps an unequal alteration of the different pituitary functions, the gonadal insufficiency being markedly accentuated. The fundamental difference between the cases of rudimentary ovaries and the case here reported is the lack of hypophyseal gonadotropins in our patient. Curiously enough, in 1 of the 2 cases of Turner's syndrome in males previously reported, serum gonadotropins were not found to be increased; but it must be stated that the method employed (25) could detect only gross increases over the normal values. Two possible explanations can be claimed to interpret our patient's disturbances: a) it may be a primary testicular insufficiency even if there is no increase in the hypophyseal gonadotropins; in fact, this increase does not seem to be absolutely constant in primary gonadal insufficiency (Wilkins and Fleischmann (13)), or b) the gonadal insufficiency may be the result of congenital hypophyseal disturbance. In this case our patient may be one more example of a predominant deficiency in the gonadotropins of the hypophysis, since the other functions of the hypophysis seem comparatively less affected.

SUMMARY

This report concerns the case of a 10-year-old boy with the same characteristics described by Turner in females, namely, delayed growth, webbing of the neck, cubitus valgus and retarded sexual development. The biopsy

of the testis revealed no evidence of Leydig cells and a static stage in the development of the germinal epithelium at the level of basal spermatogonia, whereas the Sertoli cells were well developed. Hypophyseal gonadotropins in the urine could not be detected even in small amounts; the 17-ketosteroids were slightly low. The insulin tolerance curve showed a hypoglycemia response which was within the range of normal. It is suggested that this clinical case could be considered as the homologue of the so-called syndrome of "rudimentary ovaries" in females.

REFERENCES

1. Turner, H. H.: A syndrome of infantilism, congenital webbed neck, and cubitus valgus, *Endocrinology* **23**: 566–574, 1938.
2. Winocour, P.: Peso y talla de los escolares argentinos pertenecientes a la ciudad de Buenos Aires, *Rev. Hig. y Med. escol.* **1**: 72–108, 1949.
3. Fraser, R.; Albright, F., and Smith, P.: The value of the glucose tolerance test, the insulin tolerance test and the glucose insulin tolerance test in the diagnosis of endocrinologic disorders of glucose metabolism, *J. Clin. Endocrinol.* **1**: 297–306, 1941.
4. Todd, T. Wingate: Atlas of Skeletal Maturation, Vol. I. St. Louis, The C. V. Mosby Co., 1937.
5. Repetto, O. M., and Trewes, A. A.: La determinación de los 17-cetosteroides neutros. Un nuevo aparato para su extracción de la orina, *An. Asoc. quim. argent.* **35**: 5–20, 1947.
6. Talbot, N. B.; Butler, A. M.; Berman, R. A.; Rodriguez, P. M., and MacLachlan, E. A.: Somatic and endocrine studies of puberal and adolescent boys. VII. Excretion of 17 ketosteroids by normal and by abnormal children, *Am. J. Dis. Child.* **65**: 364–375, 1943.
7. Raices, A. E., and Rivara, L. T.: La eliminación de 17-cetosteroides en niños, *Semana méd.* **54**: 856–859, 1947.
8. Klinefelter, H. F.; Albright, F., and Griswold, G. C.: Experience with a quantitative test for normal or decreased amount of follicle-stimulating hormone in the urine in endocrinological diagnosis, *J. Clin. Endocrinol.* **3**: 529–544, 1943.
9. Capurro, A. M.: Una nueva forma clinica de infantilismo.—"Sindrome de Turner." Tesis de Doctorado en Medicina, Universidad Nacional de Buenos Aires, Facultad de Ciencias Médicas, 5321, 1940.
10. Varney, R. F.; Kenyon, A. T., and Koch, F. C.: An association of short stature, retarded sexual development and high urinary gonadotropin titers in women; ovarian dwarfism, *J. Clin. Endocrinol.* **2**: 137–145 (March) 1942.
11. Albright, F.; Smith, P. H., and Fraser, R.: A syndrome characterized by primary ovarian insufficiency and decreased stature, *Am. J. M. Sc.* **204**: 625–648, 1942.
12. Schneider, R. W., and McCullagh, E. P.: Infantilism, congenital webbed neck and cubitus valgus (Turner's syndrome), *Cleveland Clinic Quart.* **10**: 112, 1943.
13. Wilkins, L., and Fleischmann, W.: Ovarian agenesis: pathology, associated clinical symptoms and the bearing on the theories of sex differentiation, *J. Clin. Endocrinol.* **4**: 357–375 (Aug.) 1944.
14. Del Castillo, E. B.; de la Balze, F. A., and Argonz, J.: Syndrome of rudimentary ovaries with estrogenic insufficiency and increase in gonadotropins, *J. Clin. Endocrinol.* **7**: 385–422, 1947.

15. Dorff, G. B.; Appelman, D. H., and Liveson, A.: Report of a case showing congenital defects, short stature, retarded sexual development and no urinary gonadotropins, *J. Clin. Endocrinol.* **7**: 807–811, 1947.
16. Goldberg, M. B.; Maxwell, A. F., and Smith, P.: Three unusual endocrinopathies with associated ovarian pathology. I. Ovarian agenesis. II. Precocious puberty. III. Virilism, *J. Clin. Endocrinol.* **7**: 11–29, 1947.
17. Lisser, H.; Curtis, L. E.; Escamilla, R. F., and Goldberg, M. B.: The syndrome of congenitally aplastic ovaries with sexual infantilism, high urinary gonadotropins, short stature and other congenital abnormalities. Tabular presentation of twenty-five previously unpublished cases, *J. Clin. Endocrinol.* **7**: 665–687, 1947.
18. Flavell, G.: Webbing of neck with Turner's syndrome in male, *Brit. J. Surg.* **31**: 150–153, 1943.
19. Greenblatt, R. B., and Nieburgs, H. E.: Turner's syndrome, *J. Clin. Endocrinol.* **8**: 993–1003, 1948.
20. Maranon, G.: Naevi y secreciones internas, *Prensa méd. argent.* **25**: 1033–1036, 1938.
21. Albright, F.: A classification of the causes of hypoleydigism, *Tr. A. Am. Physicians.* **43**: 1–11, 1941.
22. Del Castillo, E. B.; Trabucco, A., and de la Balze, F. A.: Syndrome produced by absence of the germinal epithelium without impairment of the Sertoli or Leydig cells, *J. Clin. Endocrinol.* **7**: 493–502, 1947.
23. Klinefelter, H. F., Reifenstein, E. C., and Albright, F.: Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism, and increased excretion of follicle-stimulating hormone, *J. Clin. Endocrinol.* **2**: 615–627, 1942.
24. Heller, C. G.; Nelson, W. O., and Roth, A. A.: Functional prepuberal castration in males, *J. Clin. Endocrinol.* **3**: 573–588, 1943.
25. Fluhmann, C. F.: The significance of anterior pituitary hormone in the blood of gynecologic patients, *Am. J. Obst. & Gynec.* **20**: 1–15, 1930.

AN UNUSUAL CASE OF PRECOCIOUS PUBERTY ASSOCIATED WITH OVARIAN DYSGERMINOMA

A. M. HAIN, PH.D., D.SC.

From the Department of Obstetrics and Gynecology, Manchester University, Manchester, England

A DESCRIPTION is given of the only case of precocious puberty associated with dysgerminoma in which hormonal assays have been carried out. The author is indebted to Professor Macafee and Professor Allen, both of Belfast, for permission to describe it.

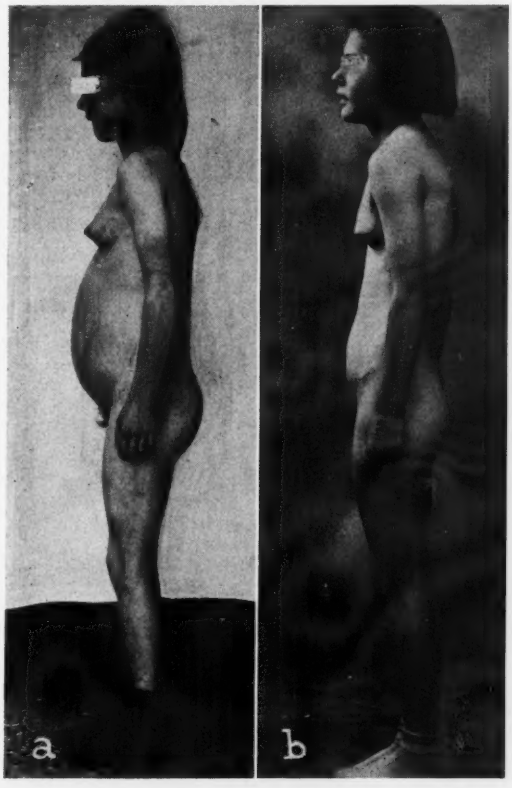


FIG. 1. *a*. The patient, a girl aged 8, with sexual precocity associated with a dysgerminoma. Fluid collected again rapidly after paracentesis.
b. The patient a year after operation, showing marked regression of symptoms of precocity.

Received for publication, February 19, 1949.

The patient, aged 8 years, was admitted to hospital on June 22, 1948, with a history of swelling of the breasts and growth of axillary and pubic hair for two years. She had the general appearance of a girl of 12 (Fig. 1), though ossification (wrists) showed an age of about 7 or 8; breast development was equal to that of a girl of 16 or 17. There were no signs of virilism other than some facial acne. There had been intermittent vaginal bleeding for the past six months, and simultaneously the abdomen had slightly increased in size; during the week prior to admission to hospital this increase had been very marked. A paracentesis was immediately performed and 11 pints of straw-colored fluid were drawn off, after which it was possible to palpate a large, hard tumor which appeared to arise from the pelvis.

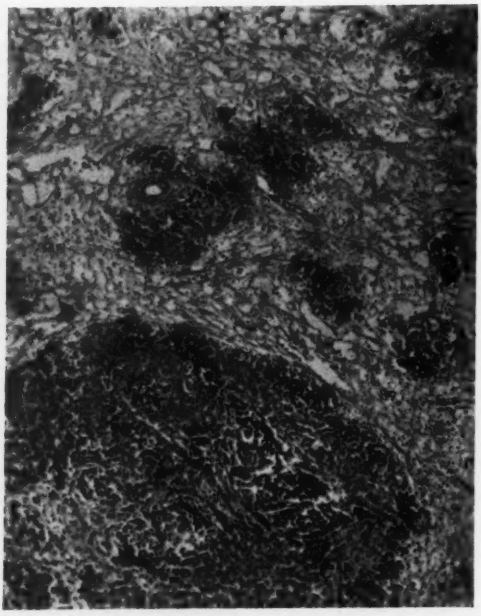


FIG. 2. Dysgerminoma in patient seen in Figure 1. Section of tumor showing large groups of cells set in a matrix of loose connective tissue. Lack of homogeneity; arrangement is in strands or clumps of large cells. ×50.

As an aid to diagnosis of the tumor the patient's hormone excretion was investigated. The 17-ketosteroid output, at 8.4 mg./24 hrs., was only slightly in excess of the normal for a child of 8; and this fact, together with the excessive feminization and absence of masculinization made a tumor of adrenal cortical origin unlikely, though not disproven. However, the significant fact in the hormonal findings was *a strongly positive reaction to the Aschheim-Zondek test,* which caused a provisional diagnosis to be made of ovarian carcinoma of teratomatous or chorionic type.

Operation was performed on June 26, 1948, by Professor Macafee. A mid-line subumbilical incision was made and free fluid escaped. A pedunculated tumor measuring $4 \times 3 \times 2\frac{1}{2}$ inches replaced the left ovary. It was reniform in shape, semisolid and made

up of fibrous and fleshy parts, with a surface that was smooth and mottled in appearance. The pedicle, consisting of tube and broad ligament, was clamped, divided and ligated and the tumor removed. The right ovary was normal, but the uterus was of adult size and the endometrial glands were in an active proliferative stage of development. There was no evidence of any metastases in the liver or peritoneum.

Histologic description of the tumor

The ovarian tumor was studied in multiple sections, being sampled with seven blocks, all of which were essentially similar. I am indebted to Dr. Langley, Pathologist to this Department, for the following histologic description:

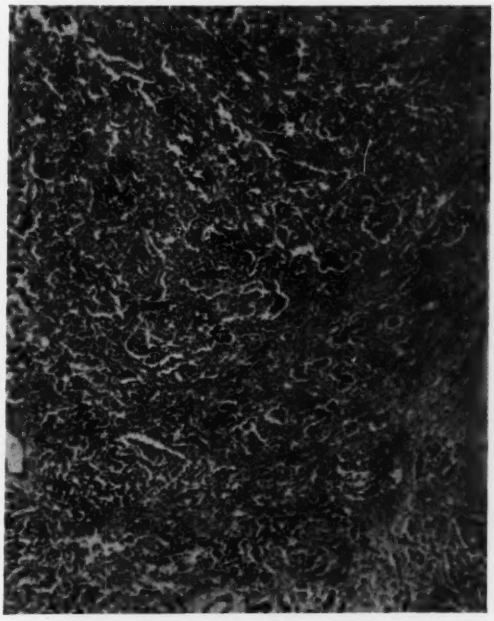


FIG. 3. Connective tissue framework infiltrated by small round cells (lymphocytes). ×50.

"The tumor consists of large groups of cells set in a matrix of loose connective tissue (Fig. 2). The groups of cells are not homogeneous but consist sometimes of strands of large cells, and at others, of clumps of 40 to 100 such cells arranged in a connective tissue framework. Between these strands or clumps the tissue is infiltrated by small round cells, probably lymphocytes (Figs. 3 and 4). The nuclei of the large cells have a clearly defined nuclear membrane and the chromatin is present as large granules with clear intervening nucleoplasm. Two to four nucleoli may be seen. There is variation in nuclear structure, some nuclei being hyperchromatic and others showing mitotic figures (Fig. 5). The cytoplasm of these cells forms a rim round the nucleus and is eosinophilic and granular. Scattered throughout the tumor are groups of multinucleated giant cells. In

FIG. 4. Section showing groups of multinucleated giant cells, some of which are seen abutting the connective tissue septum. No tubules or lumina present. ×75.

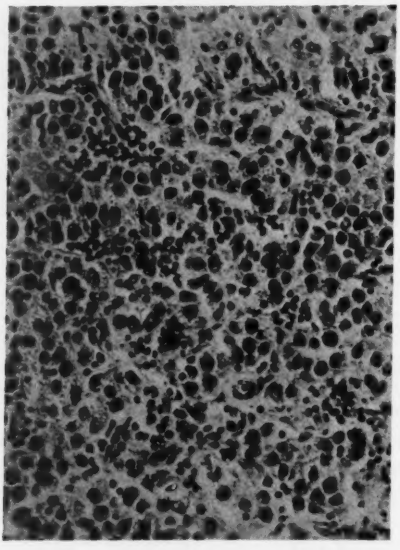


FIG. 5. The nuclei of large cells have clearly defined nuclear membrane; 2–4 nucleoli may be seen, and some mitotic figures; also giant cells. ×290.

Figure 4 a number of these can be seen abutting the connective tissue septum. None of these cells resembles Sértoli or Leydig cells, nor are lumina or tubules present in any of the cords.

The structure is that of a large spheroidal cell carcinoma of seminoma-like appearance and hence is a dysgerminoma.

Graafian follicles are present in various stages of maturation (Fig. 6) thus indicating that follicular activity is not suppressed."

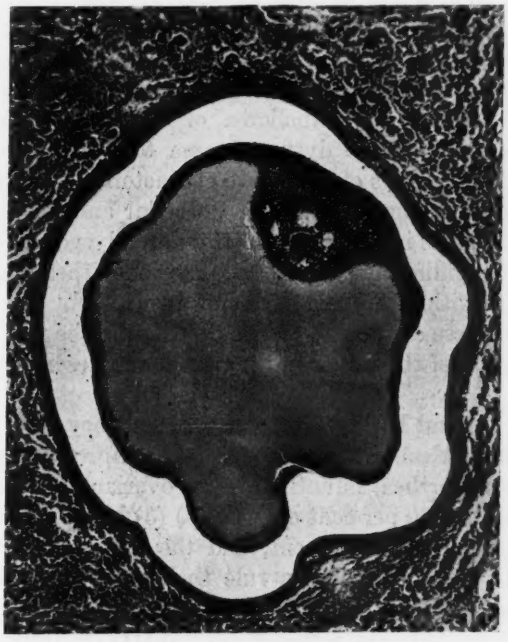


FIG. 6. Mature Graafian follicle. ×40.

Postoperative progress was good. When the patient was seen ten weeks later, it was noted that pubic hair, shaved for operation, had grown again; the general impression was that the breasts were somewhat larger than before. There had been no recurrence of vaginal bleeding and her general condition was excellent.

I am indebted to Dr. A. W. Dickie, the Registrar of the Royal Belfast Hospital for Sick Children for the following report dated July 18, 1949, a year after the operation:

"She is extremely well indeed, but more remarkable still, all signs (of precocity) have very markedly regressed—her breasts are very much softer and much smaller, her pubic hair has considerably decreased, and her axillary hair has almost disappeared. There has been no vaginal staining and there were no abnormal findings at all." (Fig. 1b).

As a check on a possible recurrence of the tumor, A-Z tests have been performed at frequent intervals since the tumor was removed in June 1948. Throughout the three months following the operation an excessive secretion of follicle-stimulating hormone persisted, as shown by the fact that injection of as little as 3 cc. of the child's urine caused marked uterine enlargement in immature mice; the blood-spot reaction observed

prior to operation has never recurred and, since October 1948, even 5 cc. of urine has been entirely without hormonal effect.

DISCUSSION

Histologically the tumor is a duplicate of the false seminoma of the testicle. Meyer (1) who first called the neoplasm "dysgerminoma" emphasized that the potential capacity of the undifferentiated cells in which it originates is not known and he assumes that, to begin with, they lost the capacity for differentiation into specific germ cells. Ewing (2) describes dysgerminomas as "malignant, radiosensitive, cellular tumors, occurring at rather early ages, lacking hormonal effects. . . . They may be associated with teratoma and chorionepithelioma of the ovary." More recently Teilum (3) has assigned the dysgerminoma to a group which he calls gonocytomas, the members of which are characterized histogenetically by their common origin from a particular testicular anlage. Ovarian tumors belonging to this series in order of transition are: dysgerminoma, an intermediate (adenopapilliferous) form and chorionepithelioma, and in his opinion these transitions are suggestive of a totipotent cellular origin. In consideration of these claims the histologic detail in the microphotographs and the description of the tumor in the case herein described are of special interest.

Both Meyer (1) and Ewing (2) noted the tendency for dysgerminomas to occur in young girls and in pseudohermaphrodites; Ewing adds "others with primary amenorrhea, infantile uterus, ovarian hyperplasia or hirsuties." Yet more than 50 per cent of cases (4) (5) have occurred in individuals with normal sex development, and they have been found during, before and after pregnancy. As a rule their removal from the pseudohermaphrodite does not modify the syndrome but a unique exception is claimed by Seegar (6):—in a pseudohermaphrodite from whom a dysgerminoma was removed the tumor recurred, but it regressed after roentgen-ray therapy and the masculinizing symptoms were completely alleviated.

According to Selye (7) the tumor is exceedingly rare and represents hardly more than 1 to 2 per cent of all solid ovarian tumors, though others put the figure at 3 to 10 per cent. Moreton and Desjardins (8) state that over 300 dysgerminomas have been reported in medical literature up to 1947. As illustrating that it is a tumor of the young, Seegar, reporting 98 cases found that 44.5 per cent occurred between the ages of 10 and 19 years, with only 10 per cent in women over 40. The youngest recorded case is a girl aged 5 (9), in whom there were no abnormal sexual changes.

Few *small* tumors have been discovered, as their growth is usually rapid and the tumor attains considerable dimensions before detection. They are

highly malignant, though probably less malignant than the testicular variety. They tend to invade locally the pelvic structures and distant metastases are rare (10). Probably 20 to 35 per cent of dysgerminomas are bilateral. Some (6) claim that the unilateral tumors are generally benign, but others (11), that even these are frequently malignant. The clinical outcome is apparently adversely determined by such factors as a twisted pedicle, a torn capsule, ascites, adhesions and involvement of lymph nodules. The treatment which offers the best prospects of longevity is surgical removal followed by adequate roentgen-ray therapy such as is in use at the Mayo Clinic and outlined by Moreton and Desjardins (8).

Hormonal considerations. The tumor is believed to be hormonally indifferent, in conformity with Meyer's concept of its origin from "an undifferentiated form of germinal cells which have lost their faculty of becoming either masculine or feminine in type." On the other hand, careful hormonal studies have not been carried out in a sufficient number of cases, though it is beginning to be recognized that the tumor may be associated with an excess of A.P.L. substances in the urine.

In addition to the case that is the subject of this report, 5 others are on record in which dysgerminomas were associated with an excessive excretion of chorionic gonadotropin, and 1 with a high F.S.H. output (Table 1). The complete data of Hamburger's 2 cases could not be ascertained and

TABLE 1. CASES OF DYSGERMINOMA ASSOCIATED WITH EXCESSIVE SECRETION OF GONADOTROPIN

Author	Age of patient (yrs.)	Hormone test
Moreton & Desjardins (8) (case 4)	23	Friedman test positive; very large tumor with metastases.
Potter (12)	14	Friedman test positive.
Fauvet (13) (case 2)	19	A-Z test positive.
Hamburger (14) (cited by Teilum (3))	?	50,000 M.U. chorionic gonadotropin
Hamburger (14) (cited by Teilum (3))	?	1,000 M.U. chorionic gonadotropin
Wallis (15)	17	150–200 M.U. follicle-stimulating gonadotropin per liter of urine.

the information has been taken from a paper by Teilum (13). Potter's case (12) is of special interest, as the Friedman test, although positive with the first tumor, was negative when the tumor recurred four years later.

In addition, 2 instances are on record in which demonstrable hormone secretion resulting from a dysgerminoma may be inferred, since precocious puberty accompanied the tumor. In neither of them were hormone investigations carried out. The case of Rendu and Pouzet (16) can be dismissed briefly as no histologic description or illustration is given. The subject was a girl aged 6, having a "seminoma du type mâle de l'ovaire développé sur un ovo-testis."

The second case of precocious puberty attended by a dysgerminoma is described by Tietze (17):—a 10-year-old girl had the usual accompaniments of the condition, namely, menstruation, breast development and growth of pubic and axillary hair; all these regressed after removal of a typical dysgerminoma. No hormonal studies were made by Tietze, and the photographs of the sections of the tumor are poor. In discussing the case, Novak (4) states that Tietze's is the only case recorded in the literature of precocious puberty due to a dysgerminoma, and he thinks that menstruation and associated signs were due to an island of granulosa-cell tumor hidden within the neoplasm and that this was overlooked. However, Novak failed to notice that Tietze's patient had features of virilism in addition to feminization, in that there was enlargement of the clitoris. The presence of nests of adrenal cortical cells within the tumor of Tietze's patient therefore remains a possibility, especially in view of the fact that 17 cases of precocious menstruation due to adrenal cortical tumors have been recorded (18).

If Tietze's case is called in question, our own Belfast case has the distinction of being the only authenticated case on record of precocious puberty due to a dysgerminoma. But since we have thrown doubt on Tietze's case on account of lack of hormonal support and the presence of features of virilism, may it not with reason be said that teratomatous or chorionic elements can have been missed in our own tumor in spite of the fact that all of the blocks prepared from it were sampled and found essentially similar? If such elements were present they would certainly account for the strongly positive reaction to the A-Z test. Furthermore cases of precocious puberty due to ovarian chorionepithelioma or teratoma are on record: Polano (19), an infant aged $1\frac{1}{2}$ years; Fasold (20), a girl aged 8; and Siegmund (21), one aged 6. In the last 2 cases the urine gave positive pregnancy reactions.

However, two considerations make it unnecessary to assume that elements other than those of the dysgerminoma gave rise to the secretory activity which caused the pregnancy test to be positive:

(a) Testicular seminomas are often associated with excessive secretion of F.S.H. (22) so that as little as 3 to 5 cc. of the patient's urine may cause marked uterine enlargement in immature mice. If the *testicular* counterpart of the ovarian "false seminoma" can be highly secretory, why should not the ovarian tumor have marked hormonal effects in some cases?

(b) Histologically the Belfast dysgerminoma bears a striking resemblance to the tumor described by Russell (23) in the brain of a boy of 10 with pubertas praecox, and called by her an "atypical teratoma." The term used by Professor Russell is one that Ewing applied to dysgerminoma which presumably may sometimes have atypical effects.

SUMMARY

A case of precocious puberty in a girl aged 8, having a dysgerminoma, is described. The urine gave a positive A-Z reaction. The tumor is a rare one and is said to be derived from undifferentiated cell structures. It occurs in individuals lacking in sexual development, but also in normal women, though chiefly in young persons. It is held to have no hormonal effects but few hormone studies have been made. Five cases besides the present one are recorded in which a positive pregnancy test has been obtained in persons with dysgerminoma. There are besides, 2 doubtful cases of precocious puberty associated with this tumor. The prognosis and treatment of such cases are touched upon.

REFERENCES

1. Meyer, R. (Berlin): Pathology of some special ovarian tumors and their relation to sex characteristics, *Am. J. Obst. & Gynec.* **22**: 697–713, 1931.
2. Ewing, J.: Neoplastic Diseases, ed. 4. Philadelphia and London, W. B. Saunders Co. 1940.
3. Teilum, G.: Gonocytoma. Homologous ovarian and testicular tumors. I. With discussion of "Mesonephroma ovarii" Schiller, *Acta path. et microbiol. Scandinav.* **23**: 242–251, 1946.
4. Novak, E., and Gray, L. A.: Dysgerminoma of the ovary, *Am. J. Obst. & Gynec.* **35**: 925–937, 1938.
5. Fauvet, E.: Über das grosszellige solide Karzinom der Keimdrüsen (Dysgerminom, Robert Meyer), *Zentralbl. f. Gynäk.* **58**: 2162–2170, 1934.
6. Seegar, G. E.: Ovarian dysgerminoma, *Arch. Surg.* **37**: 697–725, 1938.
7. Selye, H.: Textbook of Endocrinology. Montreal, *Acta Endocrinologica*, 1947.
8. Moreton, R. D., and Desjardins, A. U.: Dysgerminoma of ovary; review of 11 cases of proved tumor with special reference to radiosensitivity, *Am. J. Roentgenol.* **57**: 84–90, 1947.
9. McNally, P. A.: Dysgerminoma of ovary in child of 5 years with acute torsion of the pedicle, *J. Obst. & Gynaec. Brit. Emp.* **52**: 193–194, 1945.
10. Prendergrass, E. P., and Selman, J.: Dysgerminoma of ovary with widespread metastases, *Radiology* **46**: 377–379, 1946.

11. Greenblatt, R. B., and Pund, E. R.: Dysgerminoma ovarii, *Am. J. Obst. & Gynec.* **35:** 667–675, 1938.
12. Potter, E. B.: Dysgerminoma of the ovary, *Am. J. Path.* **22:** 551–564, 1946.
13. Fauvet, E.: Zur Klinik des Disgerminoms, *Zentralbl. f. Gynäk,* **60:** 675–686, 1936.
14. Hamburger, C.: *in* Les hormones sexuelles (by Brouha, L.). Paris, Hermann et Cie, 1938, 345–364: cited by Teilum (3).
15. Wallis, O.: Ein Fall von Dysgerminoma ovarii, *Zentralbl. f. Gynäk.*, **57:** 729–735, 1933.
16. Rendu, A., and Pouzet, F.: Seminome de l'ovaire avec menstruation précoce chez une fillette de 6 ans, *Lyon Méd.* **138:** 187–191, 1926.
17. Tietze, K.: Klinisch-anatomische Studien am Ovarialtumor material der Kieler Frauenklinik, *Arch. f. Gynäk.* **146:** 197–231, 1931.
18. Hain, A. M.: The constitutional type of precocious puberty, *J. Clin. Endocrinol.* **7:** 171–185, 1947.
19. Polano, O.: Ovarialsarkom beim Kinde, *Arch. f. Gynäk.* **120:** 308–309, 1923.
20. Fasold, H.: Ein Teratom des Ovars mit chorionepitheliomähnlichen Metastasen als Ursache einer Pubertas praecox mit positiver Schwangersschaftsreaktion, *Ztschr. f. Kinderh.* **51:** 519–526, 1931.
21. Seigmund, H.: Pubertas praecox als Folge chorionepitheliomatöser Wucherungen, *Arch. f. Gynäk.* **149:** 498–514, 1932.
22. Hamburger, C.: On the nature of gonadotrophin in cases of malignant tumors of the testis, *Acta path. et microbiol. Scandinav.* **18:** 457–484, 1941.
23. Russell, D. S.: Pinealoma: its relation to teratoma, *J. Path. & Bact.* **56:** 145–150, 1944.

VAGINAL SMEAR GLYCOGEN: LIMITATIONS AS AN INDEX OF ESTROGEN ACTIVITY*

W. BURTON AYRE, M.D. AND J. ERNEST AYRE, M.D.

From the Cytological Laboratories, Donner Building for Medical Research, McGill University, Montreal, Canada

IT IS now established that the presence of glycogen in the vaginal mucosa is influenced by estrogen. On this basis, the number of epithelial cells in the vaginal smear containing glycogen has been used as an indicator of estrogen activity. The iodine vapor technique, described by Mack (1, 2), is an easy and convenient method of detecting the glycogen-containing cells. Mack has defined the percentage of cells in the smear which give the iodine reaction as the "glycogen index." His results with the iodine vapor technique have led him to conclude (2) that vaginal smear glycopenia is indicative of advanced or complete estrogen deficiency; and that a high "glycogen index" represents maximal estrogenic effect. It might be expected, therefore, that the activity of large doses of an estrogen administered by the intramuscular route would be reflected by a glycogen-rich smear. This did not prove to be the case.

In cytological studies on 6 women receiving large doses of stilbestrol dipropionate, it was observed that the high-cornified smear of hyperestrinism (3) was characterized by a low glycogen content. In 2 cases stilbestrol was administered continuously over a two-month period. Smears taken at regular intervals were composed of many large flat squamous cells with small pyknotic nuclei. Only an occasional glycogen-positive cell was found scattered over the field. The high level of estrogen activity which was maintained was accompanied not by a glycogen-rich smear but by a definite glycopenia.

Each of the subjects studied exhibited a normal-appearing uterine cervix. The squamous cells developing in the region of the squamo-columnar junction, however, presented evidence of the existence of a localized area of abnormal growth activity. These lesions were detected by the presence of collections of abnormal cells in smears made from cervical scrapings according to the "surface-biopsy" technique of Ayre (4). Vaginal smears were taken according to the method of Papanicolaou (5), fixed in absolute alcohol and stained for glycogen with a modified Best's carmine technique. It has been found that glycogen-staining by this method gives results similar

Received for publication May 23, 1949.

* This work was supported by a grant from the Public Health Foundation for Cancer and Blood Pressure Research, Inc., Stamford, Connecticut.

to results with the iodine vapor technique (6). Abnormal cells from the cervical lesions were consistently glycopenic but seldom appeared in the vaginal smear and, therefore, were not a significant factor in the vaginal smear glycogen studies.

The following is a detailed report on one representative case:—

Mrs. E.M., aged 36, para 1, had had a subtotal hysterectomy and bilateral oophorectomy sixteen years previously at the age of 19. This was followed by menopausal symptoms. She first came under observation in July 1948, complaining of occasional vaginal spotting. The cervical stump was normal in appearance clinically. The cervical scraping, however, showed collections of abnormal cells reflecting the presence of a small localized cervical lesion. A therapeutic attempt to influence this small lesion followed. After a short period of progesterone therapy, she was given stilbestrol. From January 2, 1949 to April 25, 1949, 3,900 mg. of stilbestrol dipropionate were given intramuscularly in 50 mg. doses administered at fairly regular intervals throughout this period. Vaginal smear glycogen studies were begun on February 14, 1949, after 1,850 mg. of the stilbestrol preparation had been administered. From this date to April 25, 1949, vaginal smears were taken on twenty-nine occasions spaced at regular intervals. These smears were stained for glycogen as described and were found consistently glycopenic.

In each case, additional vaginal smears were taken and stained with Papanicolaou's stain (7) for the study of cell morphology and cornification. These reflected the presence of hyperestrinism (3). They were composed of large numbers of superficial squamous cells, most of which (70–80 per cent) were cornified.

Mack (2) has suggested that the study of vaginal smear glycogen by the iodine vapor technique may prove "a more sensitive indicator of estrogenic activity than cell morphology." It would appear from these results, however, that when large doses of stilbestrol are administered, the "glycogen index" has definite limitations as an indicator of estrogen activity. The morphological characteristics of the cells in the smear, interpreted according to the criteria of Papanicolaou (3), provide a more accurate reflection of estrogenic activity when hyperestrinism is established.

SUMMARY

In cytological studies on 6 women receiving large doses of stilbestrol dipropionate, it was found that the highly cornified vaginal smear of induced hyperestrinism was definitely glycopenic in most instances. The percentage of cells in the smear containing glycogen—the "glycogen index"—has been used as an indicator of estrogen activity. Mack has suggested that a high "glycogen index" represents maximal estrogenic effect. The results of the present study indicate, however, that when hyperestrinism is present, the "glycogen index" is not reliable as a measure of estrogen activity. The study of cell morphology, applying Papanicolaou's criteria, provides a more accurate index.

Acknowledgments

We wish to acknowledge the technical assistance of Miss Pamela Mapleson, and to express appreciation to Charles E. Frosst & Company, Montreal, and to Ciba Company, Montreal, for the generous supplies of stilbestrol dipropionate and progesterone, respectively, used in these studies.

REFERENCES

1. Mack, H. C., and Ale, Thompson: Appraisal of estrogenic activity of the vaginal glycogen index: a comparison of oral and parenteral estrone, *J. Clin. Endocrinol.* **2**: 361–364, 1942.
2. Mack, H. C.: The glycogen index in the menopause, *Am. J. Obst. & Gynec.* **45**: 402, 1943.
3. Papanicolaou, G. N., and Traut, H. F.: Diagnosis of Cancer by the Vaginal Smear. New York, Commonwealth Fund, 1943, p. 24.
4. Ayre, J. E.: Selective cytology smear for diagnosis of cancer, *Am. J. Obst. & Gynec.* **53**: 609–617, 1947.
5. Papanicolaou, G. N.: The sexual cycle in the human female as revealed by vaginal smears, *Am. J. Anat.* **52** (Suppl.): 519, 1933.
6. Willson, J. R., and Goforth, M. L.: Effect of an excess of ingested carbohydrate upon the glycogen content of vaginal epithelium, *J. Clin. Endocrinol.* **2**: 223–225, 1942.
7. Papanicolaou, G. N.: A new procedure for staining vaginal smears, *Science* **95**: 438–439, 1942.

SMEARS FROM THE FEMALE URETHRA AND THEIR RELATIONSHIP TO SMEARS OF THE URINARY SEDIMENT

ENRIQUE B. DEL CASTILLO, M.D., JOAQUIN ARGONZ, M.D. AND CARLOS GALLI MAININI, M.D.

From the Service of Endocrine Diseases at the Hospital Rivadavia, Buenos Aires, Argentina

IN a previous paper (1) del Castillo, Argonz and Galli Mainini in 1948 reported the results of an investigation on a special aspect of the cytologic content of the urinary sediment in women. From that study we showed that:

1. The cells present in the urinary sediment of women, when this sediment is smeared, fixed and stained with Shorr's technique, are very similar to, but not identical, with the vaginal cells.
2. These cells, contrary to what can be supposed, are not vaginal cells washed out by the urinary stream. In the previous report we showed that they come from somewhere in the epithelium of the urinary tract; and the present report, which confirms our previous findings, deals with the principal sources of the mentioned cells.
3. The cytologic content of the vaginal smear and of the urine sediment, taken simultaneously from the same patient, show a striking similarity: each one undergoes the same morphologic and staining changes in relation to the absence, normal presence, or therapeutic administration of estrogens. It can be said that the urinary sediment cells like the vaginal cells, are susceptible to the estrogenic hormones. This is shown by the fact that the number, size, staining properties and morphologic characteristics of the cells observed in the sediment of the urine of normal adult women are clearly different from those observed in prepuberal girls, in women with advanced and untreated menopause, castrated women and patients with rudimentary ovaries; and also from the cells found in smears obtained from patients treated by implantation of estrogen, in whom the vaginal smears show the typical "full estrogenic" picture. The estrogenic effect on the cells found in urinary sediment has been further confirmed by the daily observation of the reversal of their morphologic and staining properties under different types of estrogenic therapy, in patients proved to be without ovarian function.

Received for publication December 1, 1948.

Since we started these studies, we have observed that the urinary sediment cells, even if they are very similar to those of the vagina, nevertheless show some slight differences in size, shape and staining properties.

It was then of interest, in view of these observations, to investigate the urinary tract in order to determine which part supplied the type of cells in the sediment of the whole urine that were shown to be influenced by estrogens. The purpose of this paper is to present our data on the cellular desquamation of the urethral mucous membrane.

MATERIAL AND METHODS

In order to obtain fresh samples from the urethra, the patient must refrain from voiding for two or three hours. Placed in the gynecologic position, the region surrounding the meatus is thoroughly washed, thus eliminating the possibility of vulvar or vaginal cytologic contamination. The sample to be smeared is obtained from the urethra by means of a simple dropper, bent at the tip, with smoothed edges to avoid damage to the easy-bleeding urethral mucosa.

A small amount of a mixture of equal parts of glycerine, alcohol and normal saline is aspirated into the dropper. The dropper is introduced into the urethral lumen to a depth of no more than 2 centimeters and is then discharged of its contents by gently pressing the dropper's rubber bulb. After a few seconds, the bulb is released and most of the discharged mixture is thus again aspirated into the dropper. The sample so obtained is squeezed out onto a slide and from this stage on, the procedure follows the lines indicated by Shorr, namely, immediate fixation in alcohol-ether for five minutes at least; staining with the single differential stain for two minutes; rinsing and drying for immediate study or mounting in damar after previous dehydration with 80–95 per cent alcohol, absolute alcohol and xylol.

Even if the whole procedure is very simple, we think it advisable to stress two points. First, the dropper should be introduced 2 centimeters into the urethra, but not further, because the purpose is to obtain smears from the epithelial walls of the urethra, mainly in its anterior part. Because of the shortness of the female's urethra, if the dropper is introduced deeper, it might enter the bladder, thus obtaining bladder urine and what is more important, preventing the collection of the cells of the anterior urethra, which are the ones that give the diagnostic value to the urine sediment. The second point to be stressed is that, in order to obtain the necessary amount of material, care should be taken that the tip of the dropper be in contact with the whole urethral circumference. In order to study comparatively the smears obtained from different sources, in many cases the sediment of the first urine voided in the morning was examined first; two or three

hours later, the urethral sample was obtained and in some cases vaginal smears were made at the same time.

RESULTS

In the urethral smears obtained by means of the described technique, the following elements can be found:

a. Leucocytes, usually in small number.
b. Erythrocytes, at times.
c. Mucus very seldom.
d. Crystals or casts, never.
e. Cells of the stratified type.

The last mentioned cells represent the desquamation of a stratified epithelium and because of their morphologic and staining properties, are identical with the great majority found in the urine sediment smear; and they are also similar to the vaginal cells.

Based on the difference in size, shape, nuclear characteristics and color, these cells can easily be classified, as are the vaginal cells, into cornified, karyopyknotic, superficial spinous, and deep spinous. As these are the same cells which constitute almost the entire cytologic content of the urine sediment smear, a complete description of each type will not be given as it can be found in the original paper on the urine sediment smear, as well as the photomicrograph of the different types.

However, we think it useful to stress the slight difference between these smears and the vaginal or urine sediment smears:

1. The number of cells in a given urethral smear obviously is less than the amount found in the whole urine sediment; and this, in turn, usually is less than the number found in the vaginal smear. We are pointing out this fact because it has been our experience that observers trained in examining vaginal smears are struck by the small number of cells found in the urethra or urine smear as compared with the number obtained in the vaginal smears. This is a point in favor of urinary smears, because the cells are not grouped together or superimposed on each other, thus permitting a simpler and better individual study of each cell.
2. The cytoplasm usually stains paler than in the vaginal cells. The nucleus is usually deeply stained and in many cases, of a bright red color.
3. When the sample is taken directly from the urethra, the smear does not contain cells from the higher parts of the urinary tract. Sometimes a very few of these cells are found in the smears of the urine sediment.

From these studies we conclude, that by far the great majority of cells found in the whole urine sediment are identical with those obtained directly from the urethral mucosa. Since we have found that the urine directly obtained from the bladder by catheterization of the urethra is devoid of these cells, it is our belief that practically all the cells which make up the cytologic content of the urinary sediment come from the anterior urethra and are the result of the desquamation of its mucous lining.

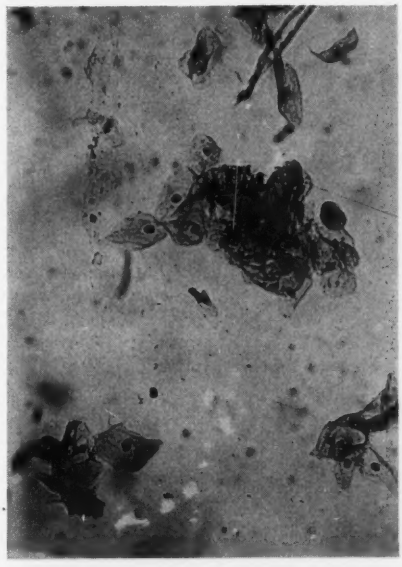


FIG. 1. Urethral smear of a normal adult woman.

Comparative studies show that when urethral and vaginal smears are simultaneously obtained from the same patient, the cytologic contents of both smears are strikingly similar. Thus, in the *normal preadolescent girl* only a few cells of the deep spinous type—small with blue cytoplasm and large nucleus—are seen. In addition, rare leucocytes might be present.

In the *normal adult woman* (Fig. 1) the karyopyknotic type of cell predominates. This cell is large and pale, with a very small and deeply stained pyknotic nucleus. The cytoplasm color ranges from light blue to pink and varies, as in the vaginal smear, according to the estrogenic level at the moment when the urethral sample is taken. This is the pattern encountered also in the urine sediment smear, but in the case of the urethral smear there is no mucus and no cells from higher places in the urinary tract. *Menopausal* urethral smears are variable but the most common picture is the

one showing thick clumps of cells of the superficial or deep spinous type, the former usually predominating and the latter varying in relation to the estrogenic deficiency. Leucocytes and mucus, very abundant in the vaginal smears, are found in only small amounts in the urethral smears (Fig. 2). As in the menopause, in cases of *secondary amenorrhea*, the pattern is

FIG. 2. Urethral smear of a woman during the menopause.

directly related to the duration and severity of the estrogenic insufficiency. In the urethral smear, the predominant cells are of the deep spinous type (small in size with a deep blue cytoplasm and a large nucleus) and of the superficial spinous type (larger, lighter stained and with a smaller nucleus) as shown in Figures 3, 4 and 5.

That the cells of the urethral smear are under the influence of the estrogens can be proved further by following their changes under the almost experimental situation of estrogen administration to patients without ovarian function. We have observed the urethral smears in some patients in the series of rudimentary ovaries studied by del Castillo, de la Balze and Argonz (2), before and during the estrogenic treatment. Usually these patients, when untreated, show an almost complete absence of cells in their smears, exceptionally some of the deep spinous cells being present: but one month later, as a result of the treatment (subcutaneous implantation of 80 mg. of estradiol benzoate in pellets), the cornified cells with a large,

FIG. 3. Urethral smear of a patient with secondary amenorrhea.

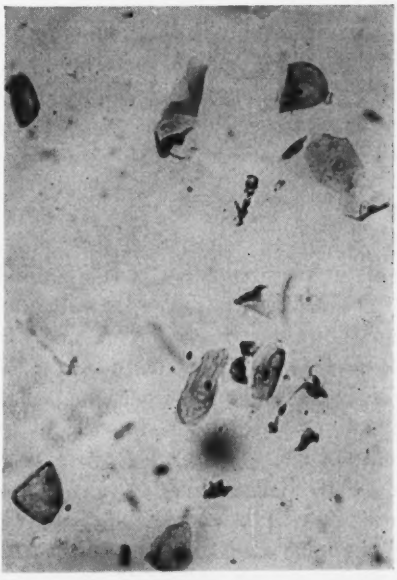


FIG. 4. Urethral smear of a patient with secondary amenorrhea, after treatment with estrogens.

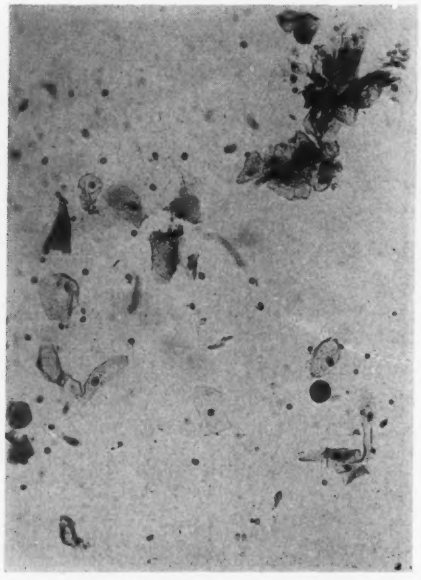


FIG. 5. Urethral smear of a patient with secondary amenorrhea—no treatment.

pink and a pyknotic nucleus, predominate. Some karyopyknotic cells with an intensely red-stained nucleus can be seen, as well as a few superficial spinous cells and a very few leucocytes (Figs. 6 and 7). The occurrence of these extremes in the same patient, leaves very little doubt on the effect of the estrogens on the epithelial lining of the urethra.

DISCUSSION

So far as we know, only males have been studied by means of urethral smears in the study of the possible effect of the sexual hormones upon the mucous epithelia of the urethra (Andrews (3) and Cohen (4) in the human, Bern and Klein (5) in the rabbit, Raynaud (6) and Starkey and Leathem (7) in the cat, and Burns (8, 9, 10) in the American opossum).

Studies on the urinary sediment have been made by Papanicolaou (11) for the diagnosis of kidney or bladder cancer and by Ludden and McDonald (12) in the case of prostatic tumors as well.

We believe that Biot and Beltran in 1944 (13) were the first to correlate the urinary sediment cells with the menstrual cycle. These authors did not use a smear technic but measured the number of cells under fixed conditions, which varied during certain phases of the menstrual cycle. Papanicolaou (14) suggested the use of the urine sediment smear for the diagnosis

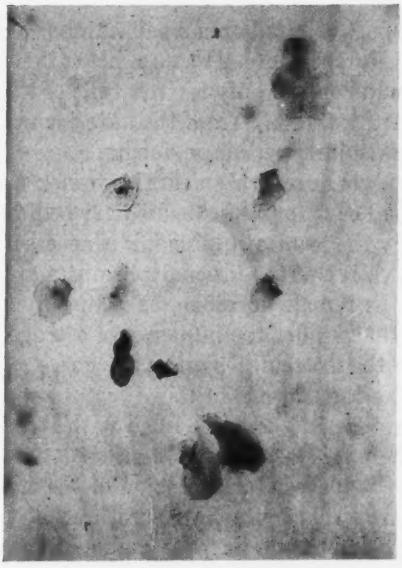


FIG. 6. Urethral smear of a patient with rudimentary ovaries, after the implantation of estradiol benzoate.

FIG. 7. Urethral smear of a patient with rudimentary ovaries, after treatment with estrogens.

of pregnancy. His report is based on a small number of patients in well advanced pregnancy. Furthermore, because he catheterized the bladder, the urine smears would contain only the few cells of the urinary tract from the bladder thus missing the cells from the anterior urethra, which are the ones of real significance in the urinary smears.

Our purpose in studying urethral smears in women was to investigate the source of the stratified cells found in the urinary sediment. In order to understand more clearly the results obtained, it is necessary to remember that the urethra is a derivative of the urogenital sinus and retains the capacity to react rapidly to the female hormone, as stated by Zuckerman (15, 16). This author claims that, under the influence of estrogens, all the epithelial structures related to the urogenital sinus undergo a process of stratification and desquamation; and in support of this, it can be recalled that the lower two-thirds of the urethra in women is lined with stratified squamous epithelium and only the upper one-third presents the transitional epithelium similar to the bladder mucosa. In the region of the trigone the epithelium is similar in character to that of the lower urethra.

These embryologic and anatomic facts enable us to interpret the process of stratification and desquamation undergone by the urethra in its lower two-thirds under the stimulus of sexual hormones. This process is similar to that induced in the vaginal mucosa, which has the same embryologic origin and similar histologic appearance.

Thus, the embryologic, histologic and experimental evidences afford the basis for a logical interpretation of the various cytologic pictures that can be found in the urine sediment and confirm the claim that this method is as reliable as the vaginal smear and in many cases can replace it with advantage.

CONCLUSIONS

1. Cells of the stratified type found in the urinary sediment of women come from the lower urethra.
2. These cells, which constitute most of the urine sediment, are similar to but not identical with the vaginal cells.
3. These urethral cells, like the vaginal cells, are influenced by the level of estrogen and their characteristics vary in accordance with it.

SUMMARY

The authors, who previously have reported that the cells of the urinary sediment (stained by the Shorr technique), are similar to and follow the same variations as do the vaginal cells, report the results of their investigation of the source of these cells in the urinary tract. A technique for obtaining material from the urethra of the female is described, as well as

the cells found, which are identical with those of the urinary sediment. These cells, of the stratified type, have been studied in patients showing various estrogenic levels and the conclusion is reached that they are as much influenced by estrogens as are the cells of the vaginal epithelium. Embryologic considerations give support to the soundness of these findings.

Acknowledgment

We are indebted to Dr. H. Selye for his kindness in helping us in the publication of this paper.

REFERENCES

1. Del Castillo, E. B.; Argonz, J., and Galli Mainini, C.: Cytological cycle of the urinary sediment and its parallelism with the vaginal cycle, *J. Clin. Endocrinol.* **8**: 76, 1948.
2. Del Castillo, E. B.; de la Balze, F. A., and Argonz, J.: Syndrome of rudimentary ovaries with estrogenic insufficiency and increase in gonadotropins, *J. Clin. Endocrinol.* **7**: 385, 1947.
3. Andrews, D. L.: A simple test for hormone deficiency in the male, *J. Clin. Endocrinol.* **6**: 516, 1946.
4. Cohen, E. J.: An evaluation of the urethral smear as an index of androgenic deficiency in the male, *J. Clin. Endocrinol.* **7**: 186, 1947.
5. Bern H., and Klein, M.: The urethral smear as an indicator of sex hormone in male rabbits, *Endocrinology* **41**: 422, 1947.
6. Raynaud, A.: Modifications apportées précocement dans la structure de la vessie et de l'urètre du chat par des injections de dihydrofolliculine, *Compt. rend. Soc. de biol.* **126**: 215, 1937.
7. Starkey, W. F., and Leathem, S. H.: Action of estrone on sexual organs of immature male cats, *Anat. Rec.* **75**: 85, 1939.
8. Burns, R. K.: Origin and differentiation of epithelium of urogenital sinus in the opossum, *Proc. Soc. Exper. Biol. & Med.* **47**: 106, 1941.
9. Burns, R. K.: Effects of female sex hormones in young opossum, *Proc. Soc. Exper. Biol. & Med.* **41**: 270, 1939.
10. Burns, R. K.: The Origin and Differentiation of the Epithelium and the Modifications Induced by Estrogens. Contribution to Embryology, No. 191. Carnegie Institution of Washington Publication No. 541; p. 63, 1942.
11. Papanicolaou, G. N.: Diagnostic value of exfoliated cells from cancerous tissue, *J.A.M.A.* **131**: 372, 1946.
12. Ludden, T. E., and McDonald, J.: Diagnosis of tumors of the kidney by cytologic investigation of urinary sediment, *Proc. Staff Meet., Mayo Clinic.* **22**: 386, 1947.
13. Biot, R., and Beltrán Nuñez, R.: Modificaciones periódicas del sedimento urinario en relación con el ciclo menstrual, *Semana méd.* **2**: 532, 1944.
14. Papanicolaou, G. N.: Diagnosis of pregnancy by cytologic criteria in catheterized urine, *Proc. Soc. Exper. Biol. & Med.* **67**: 247, 1948.
15. Zuckerman, S.: An embryological interpretation of changes induced by estrogens in the male reproductive tract, *Lancet* **1**: 135, 1938.
16. Zuckerman, S.: The histogenesis of tissues sensitive to estrogens, *Biol. Rev.* **15**: 231, 1940.

CARE AND MAINTENANCE OF TOADS AND FROGS IN CAPTIVITY, FOR THE PERFORMANCE OF GALLI MAININI'S PREGNANCY TEST

MARIA ISABEL MELLO, PHAR. D.

From the Department of Biochemistry, Oswaldo Cruz Institute, Rio de Janeiro, Brazil

HOGBEN in 1930 (1) was the first to introduce the female South African clawed frog, *Xenopus laevis* Daud. as a test animal for the diagnosis of pregnancy and recently several papers have appeared on this test and the ways of breeding the clawed frog (2, 3, 4, 5, 6, 7). Other batrachia have been tried for the diagnosis of pregnancy and Kehl in 1944 (8) demonstrated that *Discoglossus* (*anura*) from South Africa presents the same advantages as the *Xenopus*.

An investigation of the possibilities of breeding *Xenopus laevis* was started in our laboratory in September 1946 and a preliminary report on breeding and rearing *Xenopus* tadpoles was published (9). The technic of care and nourishment of the tadpoles is that recommended by Gasche (10) with slight modification. To induce spawning, the females were injected subcutaneously with a gonadotropic preparation[1] and two hours later the males were injected with half the dose given to the female. In subsequent experiments it was verified that fertilized eggs can be obtained at any time of the year. Complete metamorphosis of the tadpoles was observed within thirty to ninety days, and two pairs of this generation, *Xenopus laevis* F_1, aged 6 to 8 months were successfully mated, after injection with gonadotropic hormone from sheep hypophysis. Subsequently, four generations were mated with good results and they are still in good condition in the aquarium of the laboratory.

The action of anterior-lobe pituitary extracts on Sertoli cells and on the release of spermatozoa in *Bufo arenarum*, *Rana pipiens*, and *Discoglossus* has been known since 1929 (8, 11, 12, 13). However, this action was forgotten until the simultaneous appearance of the papers of Robbins, Parker and Bianco (14) and Galli Mainini (15). The Robbins group foresaw that the male *Xenopus* would be usable as a new test animal for the diagnosis of pregnancy and Galli Mainini proposed the use of the male toad (*Bufo arenarum* Hensel) for the same purpose. The simplicity of this test as well

Received for publication April 14, 1949.

[1] Maturon and Pregnyl were supplied through the courtesy of Dr. W. Tausk, Organon do Brazil Ltda, Rio de Janiero.

as the rapidity of obtaining positive results after the injection of untreated urine makes these animals very useful. *Bufo arenarum* as a test animal for the Galli Mainini reaction has been studied by several authors. Recently, Wiltberger and Miller suggested the use of *Rana pipiens* as a new test animal (16). Data obtained from various sources with the new reaction are summarized in Table 1.

TABLE 1

Author	Year	Test animal	Number of studied cases	Mean of error (%)
Galli Mainini (15)	1947	*Bufo arenarum* Hensel	102	—
Figueros Casas, Belizan, and Staffieri (21)	1947	*Bufo arenarum* Hensel	150	0.66
Rodrigues Lima, and Gelli Pereira (22)	1947	*B. marinus*	50	—
Mello (19)	1948	*B. marinus, B. crucifer, Leptodactylus ocellatus Xenopus and Odontophrynus*	175	2.8
Wiltberger, and Miller (16)	1948	*Rana pipiens*	—	—
Merchante (23)	1948	*Bufo arenarum*	266	2.0
Sandoval, Garcia, Colina, and Barrios (24)	1948	*Rana catesbiana*	—	—

The present paper deals mainly with the care and maintenance in captivity of certain batrachia (*Bufo marinus*, L., *Bufo crucifer* Wiel., *Odontophrynus cultripe*, Rhdt, Luetk, *Leptodactylus ocellatus* L. and *Xenopus laevis* Daud., and also describes the details of the test for diagnosis of pregnancy using these animals.

DESCRIPTION OF THE ANIMALS

Bufo toads live in swamps in the surroundings of Rio de Janeiro and can be found in almost all the states of Brazil. They are easily captured from September to March. Besides the color, size and more heavily pigmented and developed thumb, which differentiates the male from the female, it is easy to identify it by the characteristic sounds produced by the male ani-

mal in the course of manipulation. In all the species studied the male was smaller than the female.

Bufo marinus is the largest of the Brazilian toads, measuring up to 22 cm. It presents a uniformly granulated hide, yellow-olive in color. *Bufo crucifer* is smaller (7–12 cm.); it has a hard skin with the granulations and pigment divided into three transverse bands varying in color from yellow to dark brown. *Leptodacytylus ocellatus* has thickened arms and nuptial excrescences on the rudiment of the thumb. Dark spots and glandular folds are present on the olive-brown colored back of the frog (17). *Odontophrynus cultripe* is small (6–8 cm.) and presents a homogeneous, sand colored skin on the back with two regular brown spots, and a bluish abdomen. *Xenopus laevis* presents an atrophied cloaca and the anterior limb is covered with dark tissue (nuptial glove) (9).

MAINTENANCE AND CARE OF THE ANIMALS

The stock toads are kept outdoors in stone tanks measuring 4×4×3 meters and covered with a wire mesh lid. From one of the walls a trickle of tap water flows through the tank and the excess water is removed by an overflow pipe. At the bottom of the terrarium there are: wet sand, bricks with holes, green grass and stones grouped as in nature. This tank holds 50 toads. A similar tank is prepared for keeping injected animals. The environmental temperature is between 18–31° C., although in nature they live at lower temperatures. During the experiments the toads are maintained in the laboratory in individual glass jars covered with a wire mesh lid and with wet cotton and stones at the bottom.

The frogs *Leptodactylus ocellatus*, *Odontophrynus cultripe* and *Xenopus laevis* are kept separately in an aquarium the bottom of which is covered with a sand layer 4 cm. deep, some stones and aquatic plants.

The toads as well as the frogs usually eat live food (earth worms, cockroaches, flies, mosquitos, and green leaf larvae) but sometimes slices of crude liver are used. Mice may be given as food but the terrarium must be cleaned after the meals.

Banana peels should be available to attract mosquitoes and flies (drosophila). An electric lamp can be used with good results. Earthworms are put in a box containing soil and old leaves and some water to maintain dampness. In these conditions they live and reproduce normally.

THE GALLI MAININI TEST

The animal (frog or toad) is held and the urine removed from the cloaca with a round-tipped Pasteur pipette. A drop is put on a glass slide, covered with a cover slip and examined under the microscope with reduced illumination. Only leucocytes and a few cells will be seen in the urine of an unin-

jected animal. Two frogs or toads must be run for each assay as a precaution against individual variations (age, nourishment or hormonal concentration of the urine). If the animal's urine contains no spermatozoa, 10 cc. of the first morning sample of urine is injected subcutaneously. It is preferable to inject into the ventral lymphatic sac rather than the dorsal one in order to prevent the reflux of urine as well as lethal damage to the lungs. Two to five minutes after the injection, color changes are observed; *Bufo marinus* becomes dark brown or in some instances light green; *Bufo crucifer* presents a black coloration, and a beautiful blue-purple-red color is developed by *Odontophrynus*. The animals are kept separately in a glass jar as previously described. Within two hours, the urine is drawn off and examined.

If the reaction is positive, as after injection of the urine of a pregnant woman, motile spermatozoa are seen, usually isolated but sometimes in clusters; occasional epithelial cells also may be seen. The reaction leaves no doubt. If after twenty-four hours, spermatozoa are not found, the reaction is negative. In this case it is advisable to concentrate the urine and perform the test again.

RESULTS

Since March 1947, we have employed the Galli Mainini test, using the common toads and frogs found in Brazil (19). One hundred and seventy-five tests for the diagnosis of early pregnancy were undertaken. Negative results were obtained in 5 cases in which the clinical diagnosis of pregnancy was positive. When the test is performed in very early pregnancy (8–12 days after a missed menses) it is better to concentrate the urine. The urine volume injected in each toad was 1–1½ cc. per 10 Gm. of body weight depending on the species (40–100 Gm.).

The animals kept in captivity following a single injection of pregnancy urine stop eating and lose their reactivity. Animals which are well fed and used weekly, respond more quickly to the injection. The same animal can be used with one week's rest between tests for more than a year with good results, as Galli Mainini has proved.

The reaction should be performed on sexually mature animals; the maturity is ascertained by injection of a gonadotropic preparation of pregnancy urine. Animals which react in two hours to 20 M.U. (mouse units) can be used.

The motile spermatozoa appear usually within fifty minutes. However, the reaction reaches its peak from two to three hours after the administration of the hormone. Periodic examinations of the urine were made in all cases in order to detect the onset of the reaction. Fig. 1 shows the average time which elapsed before positive reactions were observed.

Robbins *et al.* (14) found *Xenopus laevis* to be satisfactory for the assay of pituitary and chorionic gonadotropins. We tried to determine the amount of hormone required to produce a positive reaction in the frog and toad studies. Increasing doses of chorionic gonadotropin were administered to 5 animals. (*Bufo marinus*, *B. crucifer*, *Xenopus* and *Leptodactylus*) and results were compared with corresponding mouse units for each dose. The urine of the test animal was drawn off within two hours. *Xenopus laevis* and *Leptodactylus ocellatus* reacted more quickly (one hour) than *Bufo marinus* and *B. crucifer* (two hours). The relationship observed for mouse and frog units was 1:3, and mouse and toad units 1:2, with chorionic preparation. This means that frogs are more sensitive than toads.

Using sheep pituitary preparations, it is possible to induce a positive

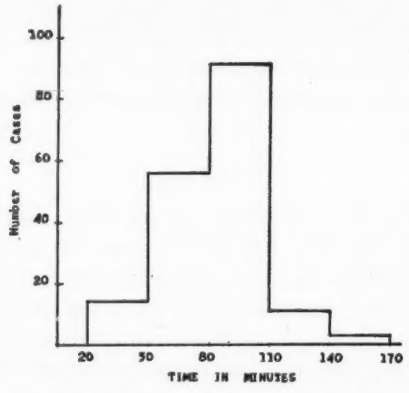


FIG. 1. Average time required for the animal reactions with pregnancy urine.

reaction with half a rat unit. These results are in agreement with those of Robbins *et al.* (14) and Weisman, Snyder and Coates (20). It will be interesting to determine whether a positive reaction can be obtained with concentrated normal urines. Investigation along this line is in progress and will be published elsewhere.

SUMMARY

Directions for the care and maintenance of toads and frogs used as test animals for the pregnancy reaction are given in detail. A description of some common species living in Brazil and used as test animals as well as the performance and results obtained with Galli Mainini's reaction in 175 cases of pregnancy are summarized. Research on the minimal doses necessary to induce spermatozoa detachment is reported and the applicability of this test to the normal gonadotropic hormone excretion is suggested.

Acknowledgment

We are indebted to Dr. Bertha Lutz for the zoologic determination of the studied frogs and toads.

REFERENCES

1. Hogben, L.: History of the Hogben test, *Brit. M. J.* **2**: 554, 1946.
2. Shapiro, H. A., and Zwarenstein, H.: A rapid test for pregnancy on Xenopus laevis, *Nature, London* **133**: 762, 1934.
3. Weisman, A. I., and Coates, C. W.: The frog test (Xenopus laevis) as a rapid test for early pregnancy, *Endocrinology* **28**: 141, 1941.
4. Coates, C. W., and Weisman, A. I.: Pregnancy test frogs being bred at will, *J.A.M.A.* **124**: 461, 1944.
5. Aronson, L. R.: Breeding Xenopus laevis, *Am. Natural.* **78**: 131, 1944.
6. Landgrebe, F. W., and Samson L.: The Hogben pregnancy test with a note on the breeding of Xenopus for the test, *J. Obst. & Gynec. Brit. Emp.* **51**: 133, 1944.
7. Herring, L. C.: Use of Xenopus laevis for pregnancy testing, *Am. J. M. Technol.* **10**: 83, 1944.
8. Kehl, R.: Études de quelques problèmes d'endocrinologie génitale chez un batracien Nord-Africaine (Discoglosse), *Rev. canad. de biol.* **3**: 29, 1944.
9. Mello, M. I.: Generalidades sôbre a "Xenopus laevis," animal reativo para ó diagnóstico precoce da gravidez, *Hospital* (Rio de Janiero) **32**: 327, 1947.
10. Gasche, P.: Die Zucht von Xenopus laevis Daudin und ihre Bedeutung für die biologische Forschung, *Rev. Suisse Zool.* **50**: 262, 1943.
11. Wolf, O. M.: Effect of daily transplants of anterior lobe of pituitary on reproduction of Frog (Rana pipiens Shreber), *Proc. Soc. Exper. Biol. & Med.* **26**: 692, 1929.
12. Houssay, B. A., and Lascano, G. J. M.: Relaciónes entre la hipofises y el testiculo en el sapo, *Rev. Soc. argent. de biol.* **5**: 77, 1929.
13. Rugh, R.: Release of spermatozoa by anterior pituitary treatment of the male frog, Rana pipiens, *Proc. Soc. Exper. Biol. & Med.* **36**: 418, 1937.
14. Robbins, S. L.; Parker, F. Jr., and Bianco, P. D.: The reaction of the male South African clawed frog (Xenopus laevis) to gonadotropins, *Endocrinology* **40**: 227, 1947.
15. Galli, Mainini, C.: Pregnancy test using the male toad, *J. Clin. Endocrinol.* **7**: 653, 1947.
16. Wiltberger, P. B., and Miller, D. F.: The male frog, Rana pipiens, as a new test animal for early pregnancy, *Science* **107**: 198, 1948.
17. Lutz, A.: Observações sobre batraquios brasileiros. Part I. O genero Leptodactylus Fitzinger, *Mem. Inst. Oswaldo Cruz* **19**: 139, 1926.
18. Miranda Ribeiro, A.: Notas para servirem ao estudo dos gymnobatrachios (anura) brasileiros, *Arch. Mus. Nac.* **27**: 134, 1926.
19. Mello, M. I.: Diagnóstico precoce da gravidez pela reação de G. Mainini em alguns anfíbios brasileiros, *Hospital* (Rio de Janeiro) **33**: 57, 1948.
20. Weisman, A. I.; Snyder, A. F., and Coates, C. W.: Physiology of egg extrusion in the female Xenopus frog test for pregnancy, *Endocrinology* **31**: 323, 1942.
21. Figueros, Casas, P.; Belizan, L., and Staffieri, J. J.: La reacción de Galli Mainini en el diagnóstico precoz y diferencial del embarazo, *Rev. Asoc. Méd. argent.* **61**: 596, 1947.
22. Rodrigues Lima, O., and Gelli Pereira, O.: Diagnóstico biológico da gravidez utilizando o Bufo marinus macho, *An. brasil. de ginec.* **24**: 245, 1947.

23. MERCHANTE, F. R.: Contribuicion al estudio del diagnostico del embarazo por la reaccion de Galli Mainini, *Semana méd.* **55**: 2843, 49, 1948.
24. SANDOVAL, A. A. I.; GARCIA, O.; COLINA, J., and BARRIOS, R.: Diagnostico precoz del embarazo en tres horas, usando como animal reativo el macho de la Rena catesbiana, *Rev. cubana lab. clin.* **2**: 191, 1948.

THE DISTRIBUTION OF RADIOIODINE IN A PATIENT WITH METASTATIC ADENOCARCINOMA OF THE THYROID

REPORT OF A CASE

JOSEPH E. RALL, M.D.,* F. RAYMOND KEATING, JR., M.D., MARSCHELLE H. POWER, PH.D. AND WARREN A. BENNETT, M.D.

From the Division of Medicine and the Section on Pathologic Anatomy, Mayo Clinic, and the Division of Biochemistry, Mayo Foundation, Rochester, Minnesota

THE following case is reported because it throws some light upon the distribution of radioiodine in tissues other than the thyroid as well as upon the question of the accumulation of radioiodine by primary and metastatic thyroid neoplasms.

REPORT OF CASE

The patient was a man aged 55 years, who registered at the Mayo Clinic on May 14, 1948. Several years prior to admission a nodular enlargement of the thyroid had occurred and in February, 1947, subtotal thyroidectomy had been performed. The microscopic examination of the thyroid was reported to show adenocarcinoma, grade 3 (Broders' method). Subsequently, the patient had received two intensive courses of roentgen therapy, after which he gained weight and appeared to be well.

A visible swelling of the scalp had appeared about six months before admission. Roentgenograms of the skull were stated to have disclosed a metastatic lesion in the left parietal bone. The swelling subsided upon roentgen treatment. One month before admission the thyroid region again had become enlarged. This had been incised and probed, but no drainage resulted. For the preceding three weeks the patient had complained of increasing difficulty in breathing, and a rapid increase in the size of the cervical mass.

On examination a hard, irregular area was palpable in the left parietal region. A huge, irregularly shaped mass filled the entire front of the neck. It was fixed and appeared to extend below the sternum. In the center there was an ulcerated area from which a small amount of serous drainage was discharging. There was extensive pigmentation of the neck and shoulders, characteristic of previous roentgen therapy. The patient had an audible stridor and his respirations were labored.

The results of general physical examination in other respects were essentially negative. The results of laboratory studies, including urinalysis, hemoglobin, leukocyte count and flocculation test for syphilis, were negative or normal. The roentgenogram of the thorax showed a small area of nodular infiltration, which was regarded as metastatic, at the level of the first anterior interspace on the left side. The roentgenogram of the skull showed an area of malignant destruction involving the superior midportion of the left

Received for publication April 27, 1949.

* Fellow in Medicine, Mayo Foundation.

parietal bone with swelling of contiguous soft tissue. The basal metabolic rate was +21 per cent, but was not regarded as satisfactory because of the patient's respiratory difficulties. Laryngoscopic examination showed fixation of the left vocal cord. Below the level of the cords, the trachea was narrowed and markedly displaced to the left.

Tracheotomy was considered, but owing to the necrotic ulceration overlying the thyroid region as well as the enormous mass of malignant tissue obscuring the true location of the trachea, it was felt that this procedure should not be attempted. A tracer dose of radioiodine was given in order to evaluate the possibility of treating the patient with radioiodine. Approximately 21 per cent of a tracer dose accumulated in the thyroid as measured in vivo with a Geiger counter, 67 per cent of the dose being excreted in the urine over a period of three days. There was a considerable quantity of radioactivity detectable over the metastatic growth in the skull. It was not possible to distinguish between normal and malignant tissue in the neck so that the possibility of collection of radioiodine by the malignant tissue could not be evaluated in that location. In view of the patient's hopeless condition, it was decided that a trial of treatment with radioiodine would be warranted and accordingly on May 22, he was given 63 millicuries of I^{131} by mouth. He continued to have difficulty with breathing, but after administration of helium and oxygen, he appeared to improve. Approximately fifty-six hours after the administration of radioiodine, he had another severe episode of stridor, during which he died.

Necropsy findings

Necropsy was performed three and a half hours after death. Urine collected up to the time of death contained 69.1 per cent of the dose of radioiodine given, leaving approximately 19.5 millicuries of radioiodine to be accounted for, mostly in the body of the patient. To guard against undue exposure to radiation on the part of the pathologists, the entire procedure was monitored with a portable Geiger counter equipped with a count rate meter calibrated in milliroentgen equivalents per hour. Preliminary survey with this apparatus disclosed that the radiation was largely concentrated in the thyroid area. Radiation in other areas measured less than 10 m.r.e.p.[1] per hour at the surface of the skin. Dissection of the neck however, was found to involve radiation of the order of 200 m.r.e.p. per hour at the surface of the skin. However, inasmuch as this part of the necropsy required less than twenty minutes, the maximal exposure was estimated to be less than 100 m.r.e.p. Subsequent decontamination of gloves, aprons, hands, clothing and instruments was checked with the same instrument.

A roughly globoid subcutaneous mass involving the entire anterior portion of the neck and submental areas extended from the cricoid cartilage to the superior portion of the sternum. The mass, which measured 5 by 6 cm. was adherent to the skin and underlying structures. The skin was perforated by four openings, measuring 5 to 8 mm. in diameter, from which purulent necrotic tissue was exuding. The left parietal region of the skull revealed a slightly elevated, soft area, measuring 3 by 4 cm., immediately beneath the scalp and attached to the underlying bone. The skin was intact over the metastatic growth. The heart weighed 365 Gm. and showed a minimal degree of arteriosclerosis of the coronary vessels.

The edematous lungs weighed 1,190 Gm. In the right upper lobe, immediately under the pleura, were two globoid hemorrhagic tumor masses. These firm masses, which were 1 cm. in diameter, showed a peripheral zone of hemorrhage with a grayish white central

[1] M.r.e.p. = milliroentgen equivalents—physical.

region. Nodules measuring from 0.8 to 1.5 cm. were scattered throughout both lungs. The spleen, liver, adrenals, kidneys, gastro-intestinal tract and pancreas were normal.

The neck organs were removed with the necrotic cystic tumor mass which measured 8 by 7 by 10 cm. In removing the neck organs the tumor was easily torn, and many necrotic cystic spaces were exposed. The trachea was displaced 3 cm. to the right by a mass of necrotic tumor which had completely replaced the left lobe of the thyroid gland. The right lobe measured 5 by 3 by 2 cm. and its medial and superior borders were surrounded by the tumor. The cut surface of the thyroid exhibited a red-brown, lobulated,

FIG. 1. Invasion of trachea by tumor, with obstruction of lumen.

gelatinous parenchyma with white fibrous trabeculae. The sectioned surface of the tumor mass through the trachea showed an irregular pedunculated mass of tumor projecting into the trachea (Fig. 1). This necrotic mass measured 4 by 3 by 1.5 cm. and occupied about three-fourths of the lumen of the trachea. The larger tumor extended from 1.5 cm. below the cricoid cartilage to 2 cm. above the tracheal bifurcation. A second tumor mass invaded the trachea just above the bifurcation. Portions of the thyroid cartilage and tracheal cartilages were destroyed by the invasive tumor. The larynx was edematous, especially the left vocal cord and arytenoid processes. The opening between the vocal cords measured 2 by 4 mm.

The skull contained a tumor mass, measuring 3 by 4 cm., which projected about 1 cm. above the surface of the skull. This lesion replaced the bone in the left parietal region, 3 cm. from the midline of the vertex of the skull. The inner table of the skull was thin but intact. The diploe in the area was replaced by soft, dark red tumor. Immediately

beneath the tumor nodule the dura was congested, with a 2 cm. zone of hemorrhage. The brain weighed 1,445 Gm. and no lesions were found in the brain substance.

Microscopic appearance

The only relevant microscopic observations relate to the thyroid and the organs involved by metastatic growths.

Tumor from region of left lobe of the thyroid.—The major portion of the tumor was made up of pleomorphic, spindle-shaped cells arranged in sheets and bundles (Fig. 2). The tumor cells were often multinucleated with varying amounts of cytoplasm. Nuclei were distinct, and atypical mitotic figures were common. The muscles of the neck were invaded by tumor. In one region the cells attempted to form acini. The dense connective

FIG. 2. Pleomorphic primary adenocarcinoma of the thyroid simulating a sarcoma. Note the scanty cytoplasm and pericellular edema (×215).

tissue surrounding the tumor and extending into the adjacent fat showed some thickening of the walls of the vessels with a narrowing of the lumen. This reaction may have represented the effect of previous roentgen irradiation. The left lobe of the thyroid appeared to have been removed previously. There was a variable degree of necrosis throughout the tumor, which had invaded the thyroid cartilage and penetrated into the lumen of the trachea as a pedunculated mass. In this region the spindle cells were larger with more abundant cytoplasm.

The right lobe of the thyroid.—The thyroid on the right side showed invasion of the upper pole by pleomorphic tumor. The lower uninvolved portion of the gland showed numerous acini which varied in size and shape, many of which contained normal-appearing colloid (Fig. 3). The interacinar connective tissue was increased in amount and the blood vessels showed a thickening of the wall and a narrowing of the lumen. The cells lining the acini were cuboidal. Some smaller, atrophic acini were present which

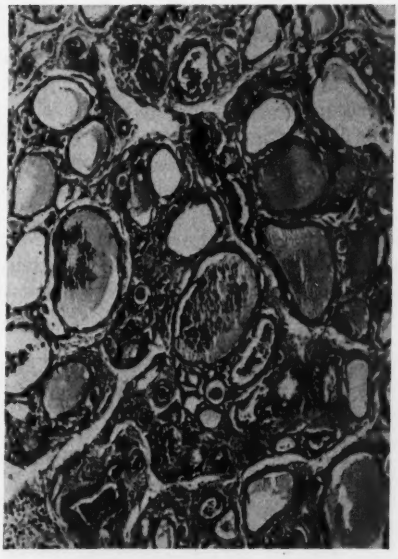


FIG. 3. Right lobe of the thyroid showing normal and atrophic follicles with interstitial fibrosis (×100).

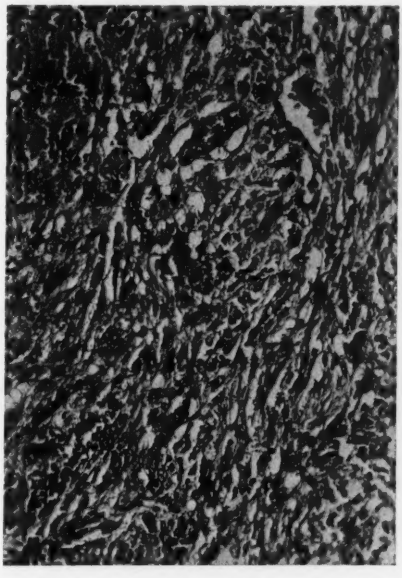


FIG. 4. Pleomorphic adenocarcinoma simulating sarcoma, from a metastasis in lung. Note the nucleoli and spindle-shaped cells (×215).

contained no colloid. The capsule of the thyroid was markedly thickened. The atrophy, fibrosis and vascular changes were typical of the changes subsequent to roentgen irradiation.

Lungs.—Scattered throughout the pulmonary parenchyma were circumscribed tumor nodules which involved the alveoli. Some of the peribronchial and alveolar lymphatics and blood vessels were filled with pleomorphic tumor cells (Fig. 4). The tumor cells in the lungs were a little more compact and less edematous than those in the neck but in other respects were similar.

Cervical nodes.—Scattered through the cervical nodes were irregular masses of spindle-shaped tumor cells. The architecture of the nodes was essentially normal except for infiltration by isolated spindle-shaped cells. In one node, focal masses of tumor cells were undergoing necrosis.

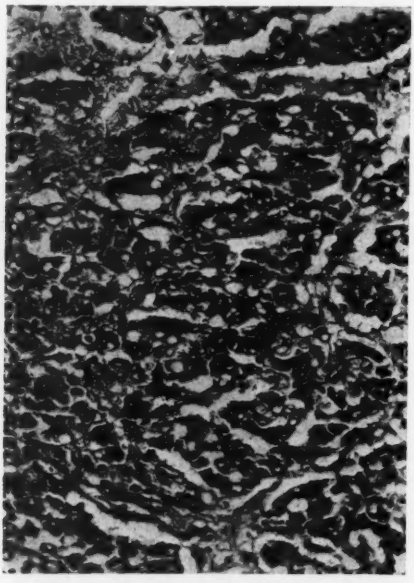


FIG. 5. Metastatic lesion in skull showing polyhedral cells in sheets with atypical acinar formation and scanty vascular stroma (×215).

Bone.—The skull showed a metastatic tumor which had destroyed much of the thickness of the bone. A few small spicules of bone were found in the tumor. This metastatic tissue was less pleomorphic and better differentiated than the cervical or pulmonary growths. The cells were polygonal and formed close compact sheets separated by scanty vascular fibrous trabeculae (Fig. 5). The cells were arranged in imperfect acini and atypical mitoses were infrequent.

ANALYSIS OF TISSUES

Total radioactivity in samples of tissue was determined by alkaline digestion, drying and counting directly under a thin window beta ray counter,

TABLE 1. DISTRIBUTION OF I^{131} IN TISSUES FIFTY-SIX HOURS AFTER ORAL INGESTION OF 63 MILLICURIES

Tissue	Total concentration of I^{131}, per cent of dose per gram of tissue $\times 10^3$[a]	Concentration of precipitable I^{131}, per cent of dose per gram of tissue $\times 10^3$	Total weight of organ, Gm.[b]	Estimated total quantity of I^{131} in organ, per cent of dose
Thyroid	2,020	1,340	—	20.0
Primary tumor	6.0	1.2	—	
Cranial metastasis	275.0	71.0	—	1.0
Pulmonary metastasis	0.09	0.11	—	
Pituitary	0.07	1.8	—	[c]
Testes	0.07	0.02	—	[c]
Adrenals	0.05	0.01	—	[c]
Pancreas	0.08	0.05	—	[c]
Red marrow	2.0	0.66	(1,500)	3.0
Brain	1.4	0.6	1,445	2.0
Liver	3.0	0.9	1,300	3.9
Kidneys	0.24	0.12	—	[c]
Muscle	0.06	0.11	(31,000)	3.3
Spleen	0.07	0.08	—	[c]
Stomach and gastro-intestinal tract	0.83	0.19	(2,400)	2.0[d]
Bladder	0.85	0.25	(150)	0.1
Blood and extracellular fluid	0.16	0.087	(17,000)	1.7[e]
Urine	—	—	—	69.1
Feces	—	—	—	(2.0)[f]
Total	—	—	—	106.1[g]

[a] Owing to insensitivity of the method used for total radioactivity, the values for the lowest concentrations (0.1×10^3 per cent per gram) are subject to large counting errors and hence are inaccurate. This may account for the disparity between total and precipitable I^{131} in pituitary, muscle and spleen.

[b] Weights given without parentheses are those obtained at necropsy. Weights in parentheses are average figures based upon body weight and average values in the literture.

[c] Quantity insignificant (that is, less than 0.1 per cent).

[d] The sample measured was stomach; the weight used applies to the gastro-intestinal tract; this figure is thus probably incorrect.

[e] The value for blood (0.16 per cent per liter $\times 5.7$ liters) was added to a value for non-precipitable I^{131} in extracellular fluid other than blood (0.073 per cent per liter $\times 11.4$ liters). This figure undoubtedly results in some duplication, as all of the tissues analyzed must to some extent have been contaminated by blood or extracellular fluid.

[f] A value of 2 per cent in feces was arbitrarily added, as this has been the average observed in such cases.

[g] The errors inherent in bookkeeping of this sort include 1) errors in sampling, 2) errors arising from contamination with blood, 3) cumulative counting errors and 4) erroneous assignment of weights when organs were not weighed at necropsy.

appropriate correction being made for self-absorption. Unfortunately this method, which measured the radioactivity in 0.2 cc. of digest, was insensitive, with the result that counts recorded in tissue containing the smallest amounts of radioiodine must be regarded as subject to a large error.

Organically bound iodine was precipitated from an alkaline digest of tissue by the method of Somogyi. The precipitate was digested and distilled in a Chaney apparatus according to a method to be described elsewhere (1). A suitable aliquot was then dried and counted with a thin-mica window beta ray counter. This method, which represented a great improvement in sensitivity over the first, provided adequate counts for all the tissues observed. Unfortunately, insufficient material was available to repeat the measurements of total radioactivity by a procedure similar to that used for precipitable radioactivity.

COMMENT

Distribution of radioiodine in tissues.—The concentration of radioiodine observed in various tissues is shown in Table 1. The relative distribution of radioiodine agrees fairly well with most data in the literature relating to the distribution of iodine (2–6). The concentrations observed in the bone marrow and cerebral cortex, however are higher than most authors report (2, 3). The liver was observed to have a relatively higher concentration of radioiodine than most nonthyroidal tissues, agreeing with previous observations. Relatively high concentrations in the endocrine glands other than the thyroid were not noted. The disparity between the figures obtained for the pituitary may possibly be explained by the fact that the analysis for total radioactivity was much less sensitive and therefore less accurate at the concentration encountered in this tissue, than the analysis for organically bound radioiodine.

Table 1 also includes a rough estimation of the total quantities of radioiodine found in various tissues, compared with the 69.1 per cent of the dose which had been observed in the urine and 2 per cent of the dose assumed to have been excreted in the feces. It was impossible to dissect out and weigh the normal thyroid tissue, but previous in vivo measurements indicated accumulation of about 20 per cent of the dose in this organ. These figures for total content are at best crude approximations, not only because of the errors inherent in the analysis employed, but also because of the possibility of serious sampling errors.

It is nonetheless rather interesting that even a rough accounting of the iodine given can be made. Keating and co-workers (7) have observed elsewhere that approximately 12 per cent of a tracer dose of radioiodine cannot be accounted for in thyroid or urine, and must therefore be considered to be distributed elsewhere (including feces). Similar calculations based on

urine and thyroid in this case leave 11 per cent of the dose unaccounted for. On the basis of the figures shown in Table 1, approximately 16 per cent of the dose appears accounted for in the tissues listed.

Radiation dosage.—The figures shown in Table 1 permit a rough preliminary estimate of the comparative quantity of radiation being received by various tissues and organs of a patient, such as the present one, who has been given large doses of radioiodine. An estimate of the rate of radiation in each tissue resulting from I^{131} in that tissue is shown in Table 2.

TABLE 2. ESTIMATED RADIATION BEING DELIVERED TO TISSUES BY I^{131} IN EACH TISSUE FIFTY-SIX HOURS AFTER ADMINISTRATION OF 63 MILLICURIES

Tissue	Microcuries of I^{131} per gram of tissue	Rate of irradiation, roentgen equivalents per day	Total tissue dose, roentgen equivalents*
Thyroid	1,260	15,200	181,000
Cranial metastases	173	2,090	24,900
Lung metastases	0.06	0.07	9
Cervical metastases	3.8	46	548
Pituitary	1.1	13	158
Cerebral cortex	0.9	11	130
Liver	1.9	23	274
Kidneys	0.15	1.8	22
Adrenals	0.03	0.4	4
Bone marrow	1.26	15	182
Testes	0.04	0.5	6
Muscle	0.04	0.5	6
Pancreas	0.05	0.6	7
Spleen	0.04	0.5	6
Stomach	0.52	6.3	75
Bladder	0.53	6.4	76

* Assuming the I^{131} concentration observed was to remain unchanged throughout the physical decay of the isotope.

These data are based upon the calculations published by Marinelli and coworkers (8, 9). A figure of 12.1 r.e.p. per day per microcurie per Gm. was employed to estimate the radiation from beta rays. The radiation contributed by gamma particles originating in that tissue may be estimated accurately only if the exact geometry of the tissue is known, but in any organ of ordinary dimensions it is probably less than 10 per cent of the radiation contributed by beta particles. A contribution from gamma rays originating in the organ equivalent to 5 per cent of that from beta particles has been arbitrarily assumed. This will probably give a slightly higher

dosage than actually occurred in small organs, such as the pituitary, but will give a smaller value for more massive tissues, such as the liver.

The radiation dosages shown in Table 2 relate *only* to radiation received by a tissue from I^{131} concentrated in that tissue, and take no account of radiation resulting from gamma rays originating in other parts of the body. Obviously, gamma rays originating from the I^{131} in each tissue will extend in all directions and penetrate every other tissue, in effect producing a nonuniform flux of gamma radiation in the body as a whole. The extent of the radiation resulting from this flux of gamma rays will depend upon the total quantity of I^{131} in the body, its location and distribution and the geometric dimensions of the body and its organs, and therefore cannot be measured. However, the average radiation resulting from the flux of gamma rays in this case at the time of death may be assumed to be of the order of 3 to 5 r.e.p. per day, perhaps substantially less in some areas, such as the limbs, and substantially more in some areas, such as the tissues adjacent to the thyroid.

It is to be noted that the relative quantities of radiation being received by various organs are valid only for the time of observation; that is, fifty-six hours after oral ingestion. Differing rates of biologic turnover of iodine in various tissues might lead to entirely different relationships at other times. Such considerations do not conceal the fact, however, that while the thyroid was being irradiated at a relatively enormous rate and some metastatic growths at what would probably be an effective rate, most tissues were receiving comparatively minimal quantities of radiation at the time of death. These figures also neglect radiation resulting from fluids, such as gastric juice and urine—both of which initially contain large quantities of I^{131}.

The collection of radioiodine by the normal and malignant thyroid tissue

The accumulation of I^{131} by the intact right lobe of the thyroid can be regarded as essentially normal and this can be used therefore as a basis of comparison with the various samples of malignant tissue examined. The primary thyroid tumor (Fig. 2) and most of the metastatic growths, especially in the lungs, represent a grade 4 adenocarcinoma of the thyroid simulating a sarcoma. The metastatic lesion in the skull was more differentiated and was forming atypical acini, which were not seen in the other tumors. Such discrepancies in the histologic appearance of thyroid tumor from various sites in the same patient have been observed before (10).

The affinity of these growths for I^{131} varied even more strikingly and in a consistent pattern. The primary lesion collected only 0.3 per cent as much I^{131} per gram as did normal thyroid tissue and yet, it should be noted, it collected more than did any nonthyroid tissue (Table 1). The pulmonary

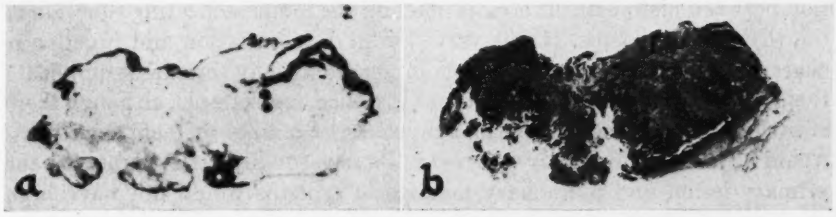


FIG. 6*a*. Autoradiogram compared with (*b*) low power photograph (×2) of primary carcinoma of left lobe of thyroid.

metastatic growths, histologically similar to the primary lesion although perhaps a little less differentiated, collected substantially no radioiodine, the amount present being in all probability no more than would result from the blood they contained. The comparatively differentiated metastatic growth in the skull, however, collected 14 per cent as much per gram as did normal thyroid and forty-six times as much per gram as the primary tumor. However, such relationships are no more accurate than the sampling on which they are based. It must be emphasized, particularly in the case of tumors which have a heterogeneous composition by reason of structure as well as the presence of necrosis, that results of tissue analysis can be very misleading.

Autoradiograms of the primary tumor (Fig. 6) show that some regions

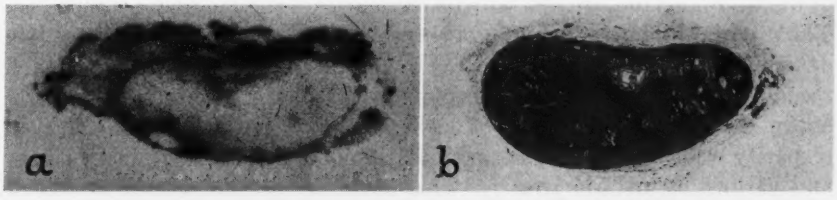


FIG. 7*a*. Autoradiogram compared with (*b*) low power (×2) photograph of metastasis in lymph node.

had apparently very little or no radioiodine in them, while others collected a discernible amount. Even after careful histologic examination, no distinction could be drawn between the tissue around the rim which picked up iodine and regions in the center which did not. An autoradiogram made from a metastatic lymph node (Fig. 7) shows the same phenomenon. In contrast, the metastasis from the skull showed apparently uniform distribution of radiation (Fig. 8).

One is justified in concluding that in this case there was some correla-

tion between histologic differentiation and the iodine-collecting function of the thyroid neoplasms. If this variation in differentiation and function is characteristic of thyroid neoplasms in general it may seriously complicate their treatment by I^{131}. In the present instance, for example, although there is little question that the normal thyroid and cranial metastatic growths would have been effectively destroyed, there is equally little doubt that the primary lesion and pulmonary metastatic growths would not have been affected unless subsequent procedures resulted in an increase in the ability to collect iodine.

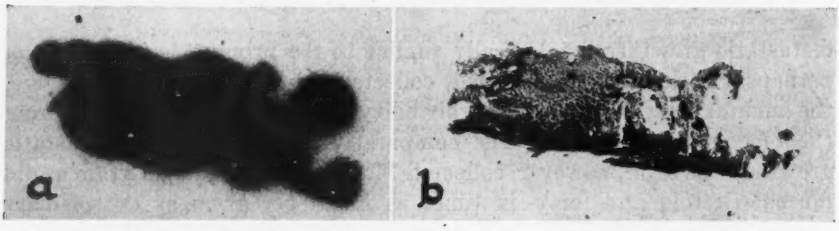


FIG. 8*a*. Autoradiogram compared with (*b*) low power (×2) photograph of cranial metastasis. Note the increased concentration of radioiodine in this metastasis, compared with the others. All autoradiograms were exposed for the same period.

SUMMARY

Clinical and necropsy data on a patient with adenocarcinoma, grade 4, of the thyroid gland, treated with 63 millicuries of radioiodine, are reported. The distribution of radioiodine in the various tissues and organs has been determined and used as a basis for estimating the quantity of radiation received by various tissues. Except for the thyroid gland and one metastatic growth, the quantity of radiation appeared negligible. Marked disparity was observed in the accumulation of iodine in the primary tumor and various metastatic growths. This could be correlated to some extent with differing degrees of histologic differentiation.

REFERENCES

1. RALL, J. E.: Unpublished data.
2. JUSTUS, J.: I. Über den physiologischen Jodgehalt der Zelle, *Virchows Arch. f. path. Anat.* **176:** 1–10, 1904.
3. STURM, ALEXANDER, and BUCHHOLZ, BRUNO: Beiträge zur Kenntnis des Jodstoffwechsels. IV. Jodverteilung im menschlichen und tierischen Organismus in ihrer Beziehung zur Schilddrüse, *Deutsches Arch. f. klin. Med.* **161:** 227–247, 1928.
4. ELMER, A. W.: Iodine Metabolism and Thyroid Function. London, Oxford University Press, 1938, 605 pp.
5. VON FELLENBERG, T.: Untersuchungen über den Jodstoffwechsel. II., *Biochem. Ztschr.* **174:** 341–354, 1926.

6. MAURER, E., and DUCRUE, H.: Zur Kenntnis des Jods als biogenes Element; der Jodgehalt im normalen tierischen Organismus, *Biochem. Ztschr.* **193**: 356–359, 1928.
7. KEATING, F. R.; POWER, M. H.; BERKSON, JOSEPH, and HAINES, S. F.: The urinary excretion of radioiodine in various thyroid states, *J. Clin. Investigation* **26**: 1138–1151 (Nov.) 1947.
8. MARINELLI, L. D.; QUIMBY, EDITH H., and HINE, G. J.: Dosage determination with radioactive isotopes. I. Fundamental dosage formulae, *Nucleonics* **2**: 56–66 (Apr.) 1948.
9. MARINELLI, L. D.; QUIMBY, EDITH H., and HINE, G. J.: Dosage determination with radioactive isotopes. II. Biological considerations and practical applications, *Nucleonics* **2**: 44–49 (May) 1948.
10. BRODERS, A. C.: Surgical pathology of the thyroid gland, *West J. Surg.* **28**: 620–632 (Oct.) 1940.

THE BEHAVIOR OF LABELED THYROGLOBULIN AND LABELED THYROXINE IN PATIENTS WITH MYXEDEMA

A. ALBERT, M.D., JOSEPH EDWARD RALL, M.D.,* F. RAYMOND KEATING, JR., M.D., MARSCHELLE H. POWER, PH.D. AND MARVIN M. D. WILLIAMS, PH.D.

From the Endocrinology Laboratory, Section on Clinical Physiology and the Divisions of Medicine, of Biochemistry and of Physics and Biophysical Research, Mayo Foundation and Mayo Clinic, Rochester, Minnesota

INITIAL observations on the behavior of radioiodocasein in a patient having myxedema have been previously reported (1, 2). We wish to add comparable observations of the metabolic fate of natural iodoprotein, thyroglobulin, and of its essential constituent, thyroxine. Although many studies of this general nature have been made in the past on man and animals (3, 4), the necessary use of pharmacologic amounts of calorigenic substances in order to obtain satisfactory determinations of iodine in body fluids has been a deterrent to further investigation. The use of the isotope method circumvents this difficulty, for it permits the use of physiologic amounts of material. Moreover, it is possible to prepare calorigenic material with sufficient radioactivity and biologic potency to enable one to obtain serial analytic data of considerably greater accuracy and sensitivity than heretofore possible, as well as serial observations in vivo. The present paper deals with the behavior of radiothyroglobulin and radiothyroxine in man, with special reference to the metabolic fate of these compounds as suggested by the nature of their excretory products.

MATERIALS AND METHODS

The investigation was carried out on 2 patients having spontaneous myxedema who volunteered for the studies. For the most part, the studies followed the same plan and employed the same procedures reported previously (2). Observations on the behavior of labeled inorganic iodide and labeled, physiologically active, organic iodine were obtained while the patients were hypothyroid. The patients were then treated, one with desiccated thyroid and the other with thyroxine, until a stable euthyroid state was attained, after which the observations on the labeled materials were repeated. All labeled materials were administered by mouth.

Received for publication April 14, 1949.

* Fellow in Medicine, Mayo Foundation.

1. Plan of Study

A. *Thyroglobulin study.*—The patient who volunteered for the study on thyroglobulin was a white married woman, aged 66 years, who had profound spontaneous myxedema of three years' duration. She had the usual signs and symptoms of myxedema consisting of pallor, dry skin, husky voice, characteristic facies and slowed tendon reflexes. The basal metabolic rate was minus 29 per cent, the concentration of cholesterol was 405 mg. per 100 cc. of serum and the electrocardiographic findings were typical of myxedema. The patient was transferred to the metabolism ward and placed on a standard repetitive diet containing a low but constant amount of iodine. The radioactive materials used in this case and the order of their administration are listed in Table 1. While the patient was myxedematous, she was given a dose of labeled sodium iodide and a week later, a dose of

TABLE 1. PREPARATIONS USED IN THYROGLOBULIN STUDY

No.	Material	Dose, mg.	Iodine, mg.	I^{131}, microcuries
1	Na I^{131} + carrier	0.12	0.1	100
2	Radioactive thyroglobulin	45	0.1	140
3	Desiccated thyroid	60	0.4	0
4	Na I^{131} + carrier	0.12	0.1	100
5	Radioactive thyroglobulin	45	0.1	140

labeled thyroglobulin. After completion of these studies, she was treated with $1\frac{1}{2}$ grains (0.1 Gm.) strong uncoated desiccated thyroid[1] until a stable euthyroid state was attained. At this time the studies with inorganic radioiodide and radiothyroglobulin were repeated. The clinical course of the patient was followed by daily observations of body weight, basal pulse and blood pressure. Basal metabolic rate and serum cholesterol were determined twice weekly. The data in Figure 1 indicate that a satisfactory response to treatment with desiccated thyroid was obtained. After completion of the study, the patient was dismissed with instructions to take $1\frac{1}{2}$ grains (0.1 Gm.) strong desiccated thyroid daily.

B. *Thyroxine study.*—The patient volunteering for the study on radioactive thyroxine was a nurse's aide, aged 24 years, who had spontaneous myxedema of three years' duration. She presented the usual history and findings of myxedema, including a puffy face, husky voice, dry skin, slowness and sensitivity to cold. The basal metabolic rate was minus 31 per

[1] Strong uncoated desiccated thyroid manufactured by Parke, Davis & Co. was used. This is assayed by its manufacturer to have a potency 50 per cent greater than U.S.P. thyroid.

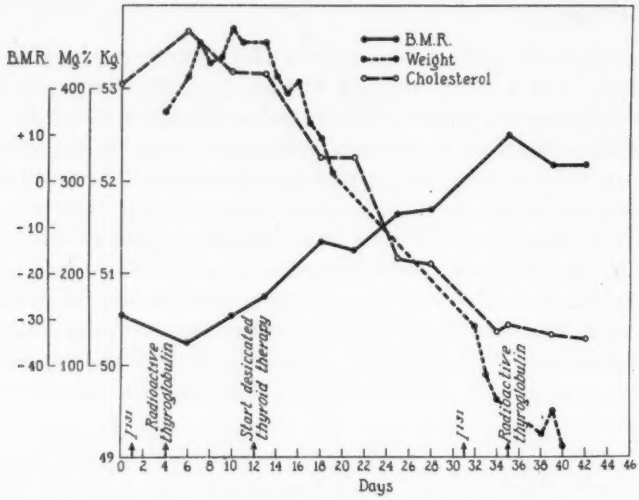


FIG. 1. Clinical course of patient 1, treated with desiccated thyroid.

cent and the concentration of cholesterol was 327 mg. per 100 cc. of serum. The patient was placed in a metabolism unit and given the same care as described for the previous patient. Before any treatment was begun, she was given a dose of labeled sodium iodide and a week later, a dose of labeled thyroxine. The characteristics of these doses are given in Table 2. After

TABLE 2. PREPARATIONS USED IN THYROXINE STUDY

No.	Material	Dose, mg.	Iodine, mg.	I^{131}, microcuries
1	Na I^{131} + carrier	0.12	0.10	100
2	Radioactive thyroxine	1.1	0.72	100
3	Thyroxine	0.5–2.0	0.3–1.3	0
4	Na I^{131} + carrier	0.12	0.10	100
5	Radioactive thyroxine	1.0	0.65	100

completion of observations, nonradioactive racemic thyroxine was given orally in alkaline solution in a dose of 0.5 mg. daily. Owing to inadequate response the dose was increased to 2 mg. of thyroxine per day until the patient became euthyroid, after which the daily dose was reduced to 1 mg. of thyroxine. The clinical response of this patient is shown in Figure 2. When euthyroidism was established the observations on labeled iodide and on labeled thyroxine were repeated. The patient was then dismissed with instructions to take $1\frac{1}{2}$ grains (0.1 Gm.) of strong uncoated desiccated thyroid daily.

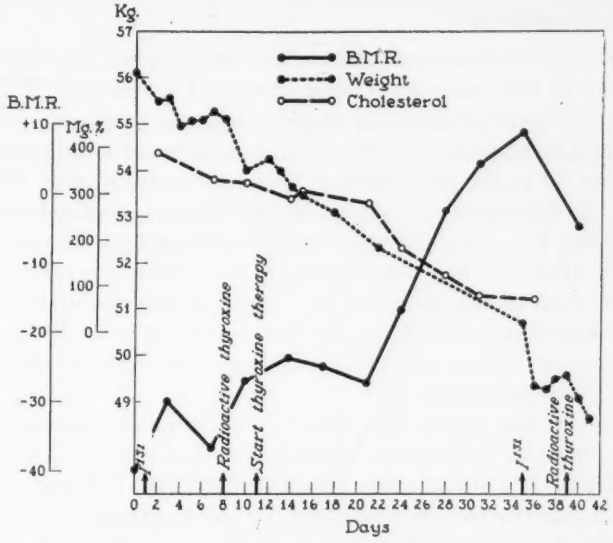


FIG. 2. Clinical course of patient 2, treated with thyroxine.

2. Preparation of Radioactive Materials

A. Inorganic radioiodide (NaI^{131})with sufficient NaI^{127} as carrier, was prepared for clinical use as described previously (2).

B. Radiothyroglobulin was prepared by injecting NaI^{131} (10 to 30 microcuries) into male rats weighing about 100 grams each and extracting the thyroids twenty-four to forty-eight hours after injection. The thyroids from about 30 rats so injected were ground in an all-glass homogenizer and suspended in 40 ml. of distilled water at pH 9.0. Iso-electric precipitations of the thyroglobulin were effected at pH 5.0 and the supernatant fluid was discarded. Two or three iso-electric precipitations were usually required to remove iodide. The preparation obtained (45 mg.) was found to be equivalent to approximately 60 mg. of strong desiccated thyroid by bioassay (5). The total organic iodine content of the preparation administered to the patient was estimated to be about 100 micrograms.

C. Radioactive thyroxine was prepared according to the method of Horeau and Süe (6), diiodothyronine[2] being combined with sufficient I^{131} to yield thyroxine with a specific activity of about 100 microcuries per milligram.[3]

[2] We are greatly indebted to Dr. K. W. Thompson, Roche-Organon, Inc., Nutley, New Jersey, for a generous supply of diiodothyronine.

[3] The radiothyroxine thus obtained and employed in this study is racemic. The possibility exists that *l*-thyroxine, the biologically active isomer, may behave differently from *d*-thyroxine, which is virtually inert.

3. Analytic Procedures

Methods for in vivo determinations and methods for determinations of radioactivity in the urine have been described previously (2, 7). Blood serum was subjected to chromate or permanganate oxidation, followed by reduction and distillation, and absorption of iodine as iodide by means of modifications (8) of the procedures of Chaney (9) and Barker (10). Radioactivity in the distillates was determined by the same method as that used for urine. Total I^{131}, precipitable I^{131} and nonprecipitable I^{131} of serum were determined. Fecal I^{131} was determined by measuring the radioactivity in aliquots of suspensions of stools by the foregoing distillation method. In several instances, precipitable I^{131} and nonprecipitable I^{131} of the feces were determined by the use of the Somogyi reagents as described by McConahey and associates (11).

Separation of the radioiodine fractions excreted in urine was effected by procedures which followed the general principles summarized by Elmer's monograph (3). Aliquots of urine were extracted with butanol and purified in the usual manner for the separation of any thyroxine which might be present. The radioactivity of the washed butanol extract was determined after removal of the solvent and solution of the residue in 1 per cent sodium hydroxide and expressed as per cent of the total radioactivity in any sample of urine. Owing to the solubility of nonthyroxine compounds in butanol during this procedure the percentage of radioactivity found in the butanol extract, minus a conservative correction of 4 per cent, was taken to represent thyroxine I^{131}. Recovery experiments with NaI^{131} and with radioactive diiodotyrosine showed not more than 2 per cent of the radioactivity in the butanol fraction could be attributed to these nonthyroxine iodine compounds. Aliquots of urine were also treated with the silver sulfate-sulfuric acid reagent (12) and alternatively with silver nitrate-nitric acid reagent (13) for the determination of iodide. These reagents precipitate 98 per cent or more of the inorganic iodide present but not significant amounts of diiodotyrosine that may be present. Thus, determination of the total radioactivity in urine before fractionation and of the thyroxine-like I^{131} and the inorganic iodide-like I^{131} in urine after fractionation made it possible to estimate by difference the diiodotyrosine-like I^{131} in urine, assuming that these three compounds exist in urine. This does not preclude the possibility that other compounds, unknown at present, may be included in these three fractions.

Chemical estimation of the protein-bound I^{127} in serum was made by foregoing modification of the distillation method (8).

RESULTS

1. Thyroglobulin

A. *Control studies with inorganic radioiodide.*—The behavior of the doses of labeled iodide before and after correction of the myxedema is shown in Figure 3. A rapid and uniform decline in radioactivity was noted over all areas measured by a Geiger counter in vivo. This decline occurred more rapidly after the patient had been brought to a normal metabolic level

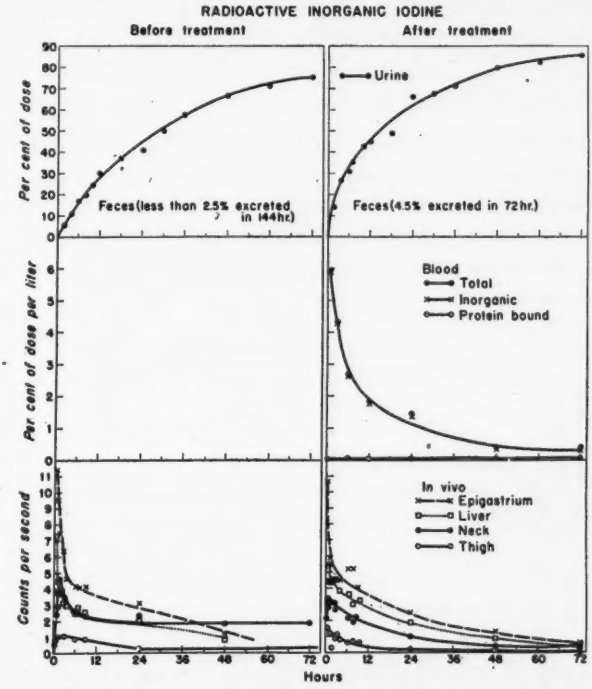


FIG. 3. Behavior of labeled iodide before and after treatment of patient 1 with desiccated thyroid.

than before. An interesting exception to this statement can be seen from the comparable curves of radioactivity measured over the neck. During hypothyroidism, a small percentage (about 2 per cent) of the dose was collected and held in the neck, presumably by remaining thyroid tissue. After treatment with desiccated thyroid, there was no demonstrable retention of I^{131} in the thyroid region.

Measurements of blood radioactivity during hypothyroidism were unfortunately lost except for the values at forty-eight and seventy-two hours after administration of the labeled iodide. At these times, the levels

TABLE 3. SERUM PRECIPITABLE IODINE AT INTERVALS AFTER ADMINISTRATION OF RADIOACTIVE INORGANIC IODINE IN THYROGLOBULIN STUDY

Hours	Micrograms per 100 cc.	
	Before treatment	After treatment
0	1.5	8.0
6	2.0	7.0
12	1.0	8.0
24	2.0	8.0
48	2.0	8.0

of the total radioactivity in blood were similar to those previously reported (1, 2) in myxedematous persons, but the percentage of precipitable I^{131} was more than half of the total serum I^{131}. At a normal metabolic level none of the serum I^{131} was in precipitable form. Eighty to 85 per cent of the dose appeared in the urine and the expected small amounts (2 to 4 per cent of the dose) in the feces.

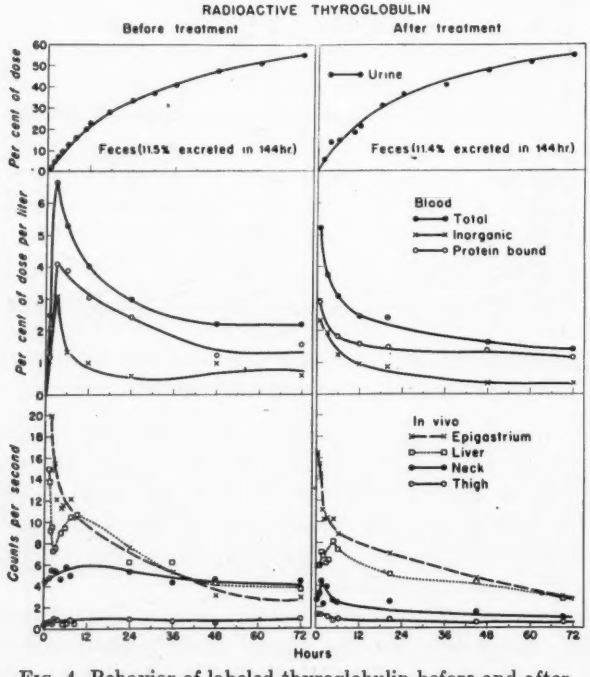


FIG. 4. Behavior of labeled thyroglobulin before and after treatment of patient 1 with desiccated thyroid.

The chemical estimations of precipitable iodine at various intervals after administration of the doses of labeled iodide are shown in Table 3. Typical values for myxedema before treatment, and for euthyroidism after treatment, were found. There was no demonstrable effect of the administered iodide on the level of precipitable iodine.

B. *Behavior of radiothyroglobulin.*—The behavior of labeled thyroglobulin (Fig. 4) was quite different from that of inorganic iodide. High concentrations of radioactivity were noted over the regions of the liver and epigastrium, declining more slowly at a hypothyroid than at a normal metabolic level. The behavior of I^{131} in the blood was quantitatively and qualitatively similar at both levels of metabolism. In each instance, appreciable amounts, one third to one half, of the total serum I^{131} was in nonprecipitable form (largely iodide) within an hour or so of administration. The urine at the end of three days contained about 58 per cent of the dose, and over a period of six days, 11 per cent of the dose appeared in the feces. Estimation of the precipitable iodine of serum at various intervals after administration of the thyroglobulin (Table 4) did not disclose any alterations in these values as a result of the ingestion of labeled material, since the amount of iodine given was not sufficiently large to increase the blood level significantly.

TABLE 4. SERUM PRECIPITABLE IODINE AT INTERVALS AFTER ADMINISTRATION OF RADIOACTIVE THYROGLOBULIN

Hours	Micrograms per 100 cc.	
	Before treatment	After treatment
0	2.0	8.3
6	1.5	7.8
12	1.5	6.1
24	2.5	—
48	3.0	—

2. Thyroxine

A. *Control studies with inorganic radioiodine.*—After administration of iodide (Fig. 5), in vivo measurements disclosed the usual rapid fall in radioactivity over the liver, abdomen and thigh. The decline appeared to be more rapid at the higher than at the lower metabolic level. While the patient was hypothyroid a significant proportion (12 per cent) of the dose appeared to be collected by the thyroid tissue as indicated by in vivo measurements over the neck. However, after treatment with thyroxine, there

was no collection of radioiodide in the region of the thyroid. Analysis of blood I^{131} showed typical disappearance curves after administration of labeled iodide. In hypothyroidism, a small proportion (12 per cent) of the total I^{131} in blood appeared initially in the precipitable fraction. By the third day this fraction constituted all of the I^{131} remaining in serum. After treatment with thyroxine, none of the I^{131} in blood was precipitable.

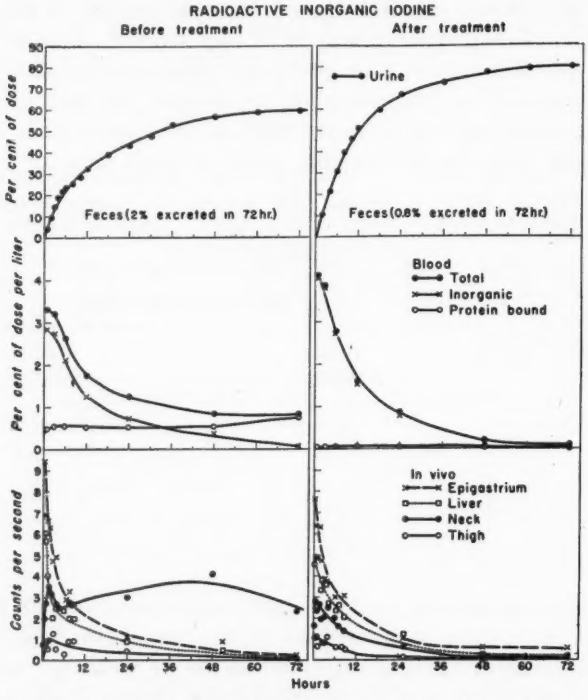


FIG. 5. Behavior of labeled iodide before and after treatment of patient 2 with thyroxine.

Before treatment the urinary I^{131} totaled 60 per cent; after treatment it totaled 80 per cent of the dose. The feces accounted for 2 per cent or less of the dose on both occasions. The chemical estimation of precipitable iodine (Table 5) did not reveal any influence of the iodide dosages on the level of precipitable iodine as measured chemically either before or after correction of hypothyroidism.

B. *Behavior of radiothyroxine.*—After the ingestion of radiothyroxine (Fig. 6) a substantial amount of radioactivity was measured over the epigastrium and over the region of the liver. The region of the thyroid did

TABLE 5. SERUM PRECIPITABLE IODINE AT INTERVALS AFTER ADMINISTRATION OF RADIOACTIVE INORGANIC IODINE IN THYROXINE STUDY

Hours	Micrograms per 100 cc.	
	Before treatment	After treatment
0	1	12
6	2	12
12	1	12
24	2	12
48	2	12

not collect appreciable radioactivity at either level of metabolism, in contrast to the behavior of labeled iodide. The blood curves of radioactivity during hypothyroidism disclosed that initially nearly all of the I^{131} of the serum was in precipitable form, after which a more or less constant concentration of nonprecipitable I^{131} appeared. At a normal metabolic rate, the same situation occurred, except that nonprecipitable I^{131} increased in

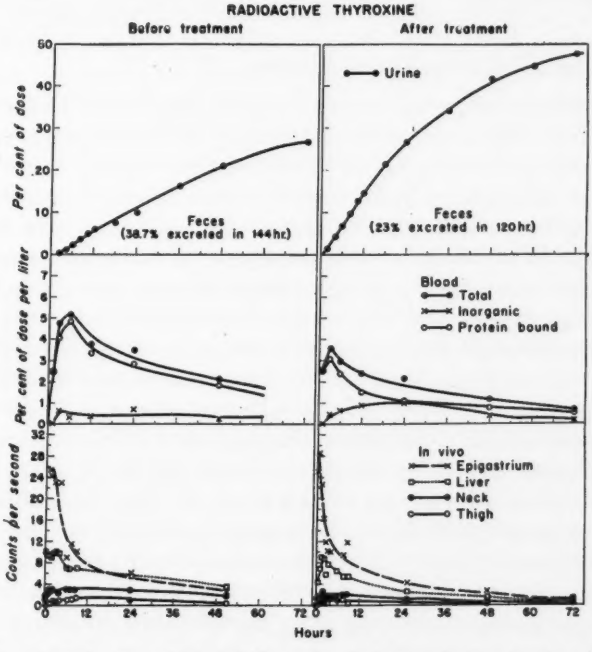


FIG. 6. Behavior of labeled thyroxine before and after treatment of patient 2 with nonlabeled thyroxine.

concentration for about two days, after which it declined. The urinary excretion by the end of the third day had totaled 28 per cent of the dose during hypothyroidism and 48 per cent during euthyroidism. Fecal excretion was 38 and 23 per cent of the dose respectively. Chemical estimation of the precipitable iodine (Table 6) did not disclose any alteration in the concentration of protein-bound iodine after the ingestion of 1 mg. of labeled thyroxine at either level of metabolism.

TABLE 6. SERUM PRECIPITABLE IODINE AT INTERVALS AFTER ADMINISTRATION OF RADIOACTIVE THYROXINE

Hours	Micrograms per 100 cc.	
	Before treatment	After treatment
0	1	12
6	1	12
12	1	12
24	2	12
48	2	11

3. Excretion of I^{131} During Tracer Studies

During the euthyroid state in both patients, feces and urine were examined to ascertain the nature of the I^{131} eliminated. The small proportion of I^{131} in feces after administration of labeled inorganic iodide in both patients was found to be almost entirely in precipitable form. The same situation was also found for the larger amounts of I^{131} excreted in the feces after either labeled thyroglobulin or labeled thyroxine was administered. These findings could represent incomplete absorption of administered organic iodine, secretion from blood into the gastro-intestinal tract or transformation of iodide liberated during digestion of the material into organic compounds by the intestinal flora. In any event, these possibilities were not resolved in the present study. There is also considerable doubt that with present methods a study of the fecal elimination of I^{131} would lead to significant information concerning the catabolism of hormonal iodine.

Fractionation of the daily urine for a period of three days after administration of inorganic radioiodide in both patients at euthyroid levels showed that 97 to 99 per cent of the I^{131} in the urine behaved as inorganic iodide. Little to none of the I^{131} appeared to behave as thyroxine, and presumably none as diiodotyrosine. However, after ingestion of radioactive thyroglobulin, only 90 per cent of the I^{131} in the first twenty-four hour urine behaved like inorganic iodide. An insignificant percentage of the I^{131} appeared in the

thyroxine-like fraction, and the remaining 10 per cent of the urinary I^{131} behaved as diiodotyrosine, being insoluble in butanol from strong base, and nonprecipitable with silver salts. During the remaining four days over which collections were made, the diiodotyrosine-like fraction decreased to an average of 5 per cent.

After administration of labeled thyroxine, 15 per cent of the urinary I^{131} appeared in the diiodotyrosine-like fraction in the first day. This organic I^{131} fraction declined to 10 per cent by the third day. Insignificant amounts of radioactivity were found in the thyroxine-like fraction. The remaining urinary I^{131} (80 to 85 per cent) behaved as inorganic iodine.

COMMENT

The behavior of labeled inorganic iodide in both patients during hypothyroidism was similar to that described in our previous study (2). Inorganic iodide was not retained by any of the tissues measured except in the neck where a small proportion of the dose (2 and 12 per cent respectively) was collected. In the euthyroid state this thyroidal collection did not occur. In both patients, a small quantity of I^{131} appeared in precipitable form in the serum after administration of inorganic radioiodide during myxedema. At a normal metabolic level none of the I^{131} in serum after administration of radioiodide was in precipitable form, a situation which is essentially the same as was found in our previous study. No completely satisfactory explanation for this behavior can be made at the present time from these studies. The behavior of I^{131} in the urine after administration of inorganic radioiodide was similar to that reported previously.

The behavior of labeled thyroglobulin and thyroxine was in general similar to that reported for iodocasein, but some exceptions and a few new observations can be noted.[4] Thyroglobulin was apparently broken down and absorbed very rapidly, since within an hour the blood contained both precipitable I^{131} and nonprecipitable I^{131} in substantial concentrations. The high concentration of radioactivity over the liver could indicate that this organ may play a part in the catabolism of iodoprotein (13). Although in general, the behavior of thyroxine was similar to that of thyroglobulin, the blood curves showed that initially nearly all of the blood radioactivity appeared in precipitable form, after which inorganic iodide was found. This suggests that thyroxine was absorbed intact, that later the molecule was attacked and that iodine was liberated. An interesting observation concerning the ability of the thyroid to collect I^{131} can be made by comparison of the labeled inorganic iodide and labeled thyroxine given during myxe-

[4] Various general aspects of the circulation and metabolism of calorigenic organic iodine compounds have been discussed in detail in our previous paper (2), and will not be repeated here.

dema. Whereas 12 per cent of the labeled inorganic iodide appeared in the thyroid, very little to none of the thyroxine I^{131} was so collected.

Another difference between the behavior of thyroxine and thyroglobulin was noted in the shapes of the curves of the urinary excretion of I^{131}. The urinary excretion curve after administration of thyroglobulin had essentially the same shape as those after administration of inorganic iodide, being exponential in form. After administration of thyroxine, however, the urinary curves appeared linear for twenty-four to forty-eight hours or more, thereafter becoming exponential. If the urinary I^{131} were entirely or largely inorganic iodide, then the initial linear urinary excretion would suggest that blood iodide was being replenished at a rate equal to or greater than the rate of disposal. This would imply the continuous and persistent release of iodide from thyroxine. The shape of the curve of inorganic radioiodide in blood during myxedema after a dose of radiothyroxine suggests that formation of iodide from thyroxine and its disposal via urine and elsewhere were almost equal. The shape of the similar curve during euthyroidism suggests that the formation of iodide exceeded its disposal for the first two days, the situation being reversed thereafter.

SUMMARY AND CONCLUSIONS

1. Comparative studies with labeled inorganic iodide in 2 myxedematous patients were made during hypothyroid and euthyroid states. During myxedema, there was localization of radioiodide only in residual thyroid tissue. At a normal metabolic level, no thyroidal accumulation occurred. A small proportion of the labeled iodide appeared in the precipitable fraction of serum during myxedema but not during euthyroidism. All of the I^{131} eliminated in the urine appeared in the form of iodide. Two to 4 per cent of the dose was excreted in the feces, all of it being organically bound.

2. Comparative studies were made with labeled thyroglobulin during hypothyroidism and euthyroidism in a patient with spontaneous myxedema. Temporary localization of radioactivity occurred over the liver. Within an hour, I^{131} appeared in the serum in both precipitable and nonprecipitable form. Fifty-eight per cent of the I^{131} appeared in the urine, of which 90 to 95 per cent was in the form of iodide. The remaining urinary I^{131} (5 to 10 per cent) behaved like diiodotyrosine. About 11 per cent of the dose was eliminated in the feces, all of it in precipitable form.

3. Similar comparative studies with labeled racemic thyroxine disclosed considerable amounts of radioactivity over the region of the liver. Radioactivity in serum was initially entirely in precipitable form, after which inorganic iodide appeared. The urinary excretion was 28 to 48 per cent of the dose and for at least two days after ingestion the curve of urinary excretion was linear in nature. Fifteen per cent of the urinary I^{131} behaved

as diiodotyrosine, and 85 per cent behaved as inorganic iodide. Twenty-three to 38 per cent of the dose was found in the feces, the radioactivity being confined exclusively to the precipitable fraction.

REFERENCES

1. HAMILTON, C. F.; ALBERT, A.; POWER, M. H.; HAINES, S. F., and KEATING, F. R., JR.: The action of iodocasein on human myxedema, with comparative studies on the fate and distribution of synthetic radioactive iodocasein and of I^{131} during hypothyroidism and euthyroidism, (Abstr.) *J. Clin. Investigation* **27**: 539 (July) 1948.
2. HAMILTON, C. F.; ALBERT, A.; POWER, M. H.; HAINES, S. F., and KEATING, F. R., JR.: The behavior of labeled iodocasein in human myxedema, *J. Clin. Endocrinol.* **9**: 828–840 (Sept.) 1949.
3. ELMER, A. W.: Iodine Metabolism and Thyroid Function. London, Oxford University Press, 1938, 605 pp.
4. SALTER, W. T.: The Endocrine Function of Iodine. Cambridge, Massachusetts, Harvard University Press, 1940, 351 pp.
5. HAMILTON, C. F.; ALBERT, A., and POWER, M. H.: Bio-assay of calorigenic substances using tadpoles of Xenopus laevis, *Endocrinology* **43**: 406–414 (Dec.) 1948.
6. HOREAU, ALAIN, and SÜE, PIERRE: Synthèse de la thyroxine marquée par le radioiode. Séparation dans les organes des divers produits iodés résultant de sa décomposition, *Bull. Soc. de chim. biol.* **27**: 483–486 (Oct.-Dec.) 1945.
7. KEATING, F. R., JR.; WANG, J. C.; LUELLEN, T. J.; WILLIAMS, M. M. D.; POWER, M. H., and MCCONAHEY, W. M.: The measurement of the iodine-accumulating function of the human thyroid gland, *J. Clin. Investigation* **28**: 217–227 (Mar.) 1949.
8. SCHNEIDER, W. A.; RALL, J. E., and POWER, M. H.: Unpublished data.
9. CHANEY, A. L.: Improvements in determination of iodine in blood, *Indust. & Engin. Chem.* (Analyt. Ed.) **12**: 179–181 (Mar. 15) 1940.
10. BARKER, S. B.: Determination of protein-bound iodine, *J. Biol. Chem.* **173**: 715–724 (Apr.) 1948.
11. MCCONAHEY, W. M.; KEATING, F. R., JR., and POWER, M. H.: The behavior of radioiodine in the blood, *J. Clin. Investigation* **28**: 191–198 (Mar.) 1949.
12. FOSTER, G. L., and GUTMAN, A. B.: On the fate of diiodotyrosine in the animal organism, *J. Biol. Chem.* **87**: 289–294 (June) 1930.
13. GROSS, J., and LEBLOND, C. P.: Distribution of a large dose of thyroxine labeled with radioiodine in the organs and tissues of the rat, *J. Biol. Chem.* **171**: 309–320 (Nov.) 1947.

METABOLIC STUDIES WITH I^{131} LABELED THYROID COMPOUNDS

COMPARISON OF THE DISTRIBUTION AND FATE OF RADIOACTIVE *d-l*-THYROXINE AFTER ORAL AND INTRAVENOUS ADMINISTRATION IN THE HUMAN*

A. ALBERT, M.D. AND F. RAYMOND KEATING, JR., M.D.

From the Endocrinology Laboratory, Section on Clinical Physiology, and the Division of Medicine, Mayo Clinic, Rochester, Minnesota

WE have been investigating the metabolism of thyroid compounds in the human by radioisotopic methods (1, 2, 3, 4). At the outset of our studies, the nature of circulating thyroid hormone was still uncertain and consequently we employed several different calorigenic compounds. These compounds were labeled with I^{131}, and physiologic doses were administered orally to myxedematous patients both while they were hypothyroid prior to treatment and while they were euthyroid after adequate replacement therapy with unlabeled calorigen. Serial measurement of urinary and fecal elimination of I^{131}, serial determinations of organic and of inorganic I^{131} in the blood, and serial in vivo measurements over several areas of the body were made. The nature of the radioiodine compounds in the urine was also studied. Three compounds—radioiodocasein, radiothyroglobulin and radiothyroxine—have been studied in this manner, and in each instance the behavior of labeled sodium iodide, equal in iodine content to the respective calorigen, was studied as a control.

The behavior of labeled sodium iodide in untreated myxedema was fairly uncomplicated. After oral administration, inorganic iodide was readily absorbed through the gastro-intestinal tract into the blood stream and was distributed largely in the extracellular fluid. The I^{131} in the blood remained in the form of iodide. It disappeared rapidly from blood into two major sites: 1) the urine, which contained a large portion of the dose; and 2) the residual thyroid tissue, if any were present, which contained a very small proportion of the dose. Except for the residual thyroid tissue which was present in some cases, no tissue showed measurable accumulation of iodide. At the end of the second or third day after oral administration,

Received for publication June 22, 1949.

* Read at the Annual Meeting of the American Goiter Association, Madison, Wisconsin, May 26, 1949.

This article will be included in the bound volume of the "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for sale early in 1950.

when the concentration of I^{131} in blood was very low, a small portion of the I^{131} became protein bound. This minute and delayed process might be interpreted as an extrathyroidal synthesis of protein bound iodine. If this interpretation is correct, it constitutes an exception to the statement that iodide was not bound by any tissue other than thyroid. In general, however, most of the administered iodide (85 to 95 per cent) was eliminated in the urine in the form of inorganic iodide. A small amount, generally less than 2 per cent of the dose, appeared in the feces. The fecal I^{131} was, however, almost entirely protein bound. At the end of the third day, which has represented our usual period of observation, the remaining iodide, or the portion of the dose unaccounted for, amounted to 5 to 15 per cent of the original dose and was probably distributed diffusely in the tissues of the body.

This same sequence of events obtained, when labeled iodide was administered to the same subjects after they had been made euthyroid by adequate treatment with the unlabeled calorigen being studied. There were, however, three points of difference in the behavior of iodide during hypothyroid and euthyroid states. First, the administered material was disposed of more rapidly when the patient was at a normal metabolic level than when he was hypothyroid, owing probably to the improved hemodynamic state that ensues after correction of myxedema. Secondly, the so-called extrathyroidal synthesis of serum protein bound iodine was entirely suppressed. Finally, if small remnants of thyroid tissue were present and had accumulated iodide during the myxedematous state, this accumulation became nil when the patient was made euthyroid. This last observation demonstrated in another way the well-known fact that sufficient exogenous thyroid medication places the thyroid at rest, at least with respect to the accumulation of iodide.

The behavior of organic iodine followed a pattern that was more or less characteristic for all three radioactive compounds studied. After oral administration, these substances were more slowly absorbed; consequently much greater radioactivity was measured over the gastro-intestinal tract. On absorption, considerable radioactivity was detected over the region of the liver for long periods. This observation is in keeping with the results reported in animals, demonstrating increased hepatic concentration and enterohepatic circulation of organic iodine compounds. This circulation may consist in secretion of material in the bile, and also liberation of iodide in the hepatic lymph. In any case, a complicated process probably occurs consisting in absorption, possible chemical transformation in the liver, secretion in the bile, reabsorption and resecretion.

The calorigenic proteins (thyroglobulin and iodocasein) were probably broken down by enzymatic digestion to smaller fragments, and as a net

effect of digestion, absorption and enterohepatic circulation, I^{131} appeared in the blood, in both organic and inorganic forms. Initially both organic and inorganic I^{131} were present in serum, but the protein bound I^{131} of the blood was usually present in larger proportion than radioactive inorganic iodide. The organic iodine of blood disappeared at a much slower rate than did iodide. Compared with labeled iodide, a much smaller proportion of the I^{131} administered in organic form was eliminated in the urine, generally less than half of the dose in the three-day period. Furthermore, after the ingestion of organic iodine compounds, 10 to 15 per cent of the I^{131} in the urine appeared in the form of organic iodine compounds, whereas 85 to 90 per cent appeared as iodide. When labeled iodide was given, all that appeared in the urine was in the form of iodide. The fecal elimination was much greater, ranging from 11 per cent of the dose in the case of thyroglobulin to 60 per cent of the dose in the case of iodocasein. Most of the fecal I^{131} was in protein bound form. In contrast to labeled iodide, organic I^{131} was not accumulated by thyroid remnants during myxedema.

Since these results were obtained with orally administered materials, it is doubtful how far they may be applied to the metabolism of endogenous thyroid hormone. Under natural conditions, of course, thyroid hormone is secreted into the systemic circulation without first running the gamut of the gastro-intestinal tract. Consequently, studies that might lead to some insight into the endogenous metabolism of thyroid hormone should employ intravenous injection of labeled material. Since the foregoing observations were made, the work of Taurog and Chaikoff (5) and Leblond and Gross (6) has proved fairly conclusively that circulating thyroid hormone is thyroxine itself. Therefore, we have extended our studies on thyroxine and are now presenting a comparison of the distribution and metabolic fate of radioactive *d-l*-thyroxine when given orally and when given intravenously to hypothyroid patients maintained at a euthyroid level by exogenous thyroid medication. The methods employed in this paper have all been described elsewhere (1, 2, 3, 4). It should be emphasized that whereas naturally occurring thyroid hormone is *l*-thyroxine, our studies have been done with racemic thyroxine. It is possible that the metabolic behavior of *d*-thyroxine may be different from that of *l*-thyroxine.

ORAL ADMINISTRATION OF RADIOACTIVE THYROXINE

The patient studied was a myxedematous woman, aged 21 years, who was effectively treated orally with 0.5 to 1.0 mg. of racemic thyroxine daily, until a euthyroid state was obtained (3). She was then given by mouth 100 microcuries of labeled sodium iodide and a week later, 100 microcuries of labeled *d-l*-thyroxine (1.0 mg.). The data are shown in Figure 1. Labeled inorganic iodide disappeared rapidly from the gastro-intestinal tract, as

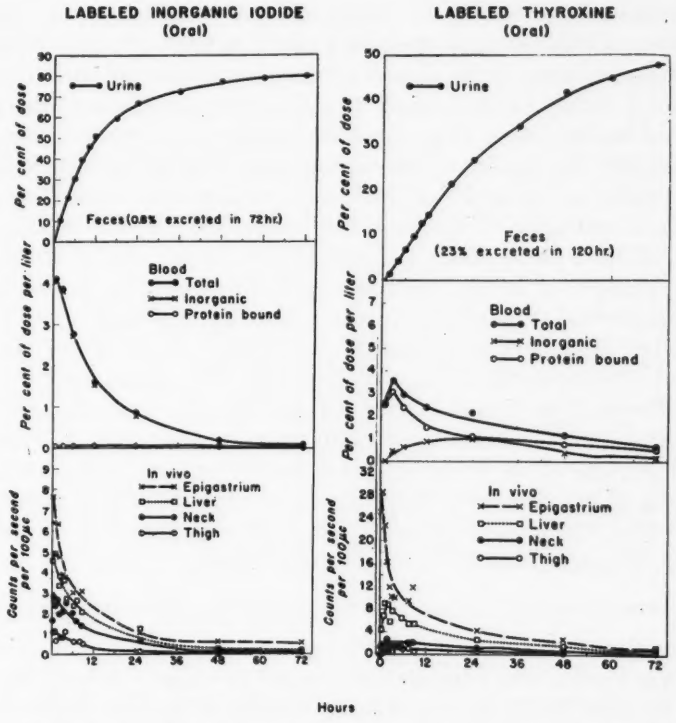


FIG. 1. The behavior of labeled, orally administered doses of iodide and of thyroxine in a myxedematous patient maintained at euthyroid level by 1.0 mg. of unlabeled racemic thyroxine daily.

indicated by in vivo counts over the epigastrium. It was not accumulated in the neck or liver and the disappearance curves over these areas more or less paralleled the disappearance of I^{131} of the blood, as measured in vivo over the thigh. The disappearance of I^{131} from the blood as measured directly was typical for that found in treated myxedema. Almost all of the I^{131} in blood was in the form of inorganic iodide. The cumulative curve of urinary excretion was also typical in shape and magnitude for treated myxedema, about 80 per cent of the dose appearing in the urine over a three-day period. All of the I^{131} in urine behaved as iodide. The fecal excretion was less than 1 per cent of the dose, all of it in protein bound, or organic, form.

After oral administration of radiothyroxine, the shape of the disappearance curve from the stomach, as measured in vivo by a counter over the epigastrium, appeared to reflect the same events as followed administration

of a dose of labeled iodide. In magnitude, however, four times as many counts were measured at comparable periods of time. Measurements over the liver showed an accumulation of I^{131} for about six hours, and then a slow progressive decline. The amount of radioactivity, however, was always about two to three times as great as that observed after administration of labeled iodide. No significant retention of radioactivity was observed in the neck. Initially, all of the I^{131} of the blood was in protein bound form, after which small amounts of inorganic iodide appeared. The inorganic iodide concentration in blood reached a peak of about 1 per cent of the dose per liter at twenty-four hours, thereafter declining so that by the third day a negligible amount of iodide was present. The disappearance of I^{131} from the blood after administration of radiothyroxine was much slower than that observed after administration of radioiodide. The urinary excretion was quite different from that of labeled iodide. Over the three-day period, less than half of the I^{131} administered as thyroxine was excreted. Furthermore, only 85 per cent of the I^{131} in urine was in the form of iodide, most of the remaining 15 per cent behaving as diiodotyrosine and a negligible amount as thyroxine. The fecal elimination over a five-day period was 23 per cent, of which 90 per cent or more was protein bound.

INTRAVENOUS ADMINISTRATION OF RADIOACTIVE THYROXINE

The patient in whom the behavior of intravenously administered thyroxine was studied was a female cretin, aged 42 years, who had been maintained for years in a euthyroid state by desiccated thyroid. Control studies with labeled sodium iodide, shown in Figure 2, revealed essentially the same behavior as that described for orally administered inorganic iodide with the exception that the phenomena attendant on gastro-intestinal absorption were now lacking. There was, therefore, less radioactivity over the epigastrium, but about the same amount over the thigh and neck as observed after oral administration. In general then, the in vivo measurements simply reflected the disappearance of iodide from the blood and body fluids as measured in various sites of the body. The curve of radioactivity in the blood was essentially similar to that after oral administration. The I^{131} remained almost entirely as iodide and rapidly disappeared from the blood. The urinary curve was likewise similar to that after oral administration and typical for that of the athyreotic organism. Eighty-two per cent of the dose appeared in the urine over a three-day period, all of it in the form of inorganic iodide. The usual small amount (0.5 per cent of the dose) was eliminated in the feces, most of it in protein bound form.

More marked differences attended the intravenous injection of thyroxine, as compared with oral administration of thyroxine. The first sample of blood drawn twenty minutes after injection was found to have a concen-

tration of I^{131} equal to 31 per cent of the dose per liter. The concentration of the I^{131} in serum fell rapidly to 7 per cent per liter after twelve hours, and thereafter diminished at a very slow exponential rate for the eight days during which observations were made. Essentially all of the I^{131} of serum remained in protein bound form, but a small amount of iodide (0.5 per cent of the dose per liter) appeared at the third day, and thereafter in-

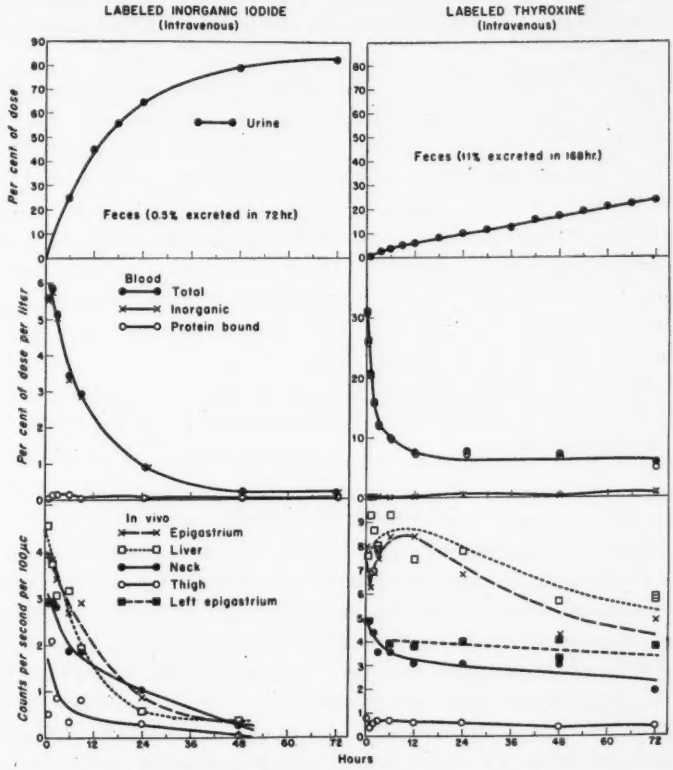


FIG. 2. The behavior of labeled intravenously administered doses of sodium iodide and of thyroxine in a cretin maintained at a euthyroid level by 0.1 Gm. of strong, uncoated, desiccated thyroid daily.

creased somewhat in magnitude. Other differences (such as the peak value of the curves, and the temporal sequence in the appearance of iodide) between the blood curves after oral and intravenous administration of radiothyroxine can perhaps be attributed to the delay in absorption, occurrence of partial digestion, and storage or transformation of the material in the liver which may occur after oral administration.

The in vivo curves were quite similar to those observed after oral administration of thyroxine, except that the initial values over the stomach were much lower. For twelve hours radioactivity accumulated over the region of the liver, and then declined. The activity over the region of the liver was several times greater than that observed in the labeled iodide control study at comparable periods. No accumulation of I^{131} was noted over the neck, and the magnitudes of I^{131} measured over the neck and thigh were not markedly different from those observed after administration of labeled iodide.

The excretion of I^{131} was somewhat different after intravenous administration of thyroxine as compared with oral administration. Twenty-five per cent of the I^{131} appeared in the urine during the first three days, and 41.3 per cent during eight days. About eighty-five per cent of the I^{131} in the urine was in the form of inorganic iodide, 10 per cent behaved like thyroxine, and the remaining 5 per cent or less appeared to behave as diiodotyrosine. Although there is uncertainty as to the exact nature and magnitude of the two organic I^{131} fractions recovered in urine, there was general agreement in the two experiments (orally and intravenously administered thyroxine) in that a small organic fraction, about 15 per cent, was excreted in the urine. Eleven per cent of the dose appeared in the feces during the week following intravenous administration of radiothyroxine, most of it as precipitable iodine.

ANALYSIS OF CURVES

Methods have previously been described for estimating rates of disappearance from various curves of radioactivity following the administration of inorganic radioiodine. In the case of orally administered calorigenic compounds, the complexities introduced by alimentation appear at present sufficiently large to preclude analyses by such means. However, observations following intravenous administration of radiothyroxine, especially when extended over a period of eight days, are amenable to kinetic analysis. It becomes evident that, as in the case of inorganic radioiodide, radiothyroxine is disposed of at an orderly and constant rate, and the curves constructed from observations on the urine and the blood and from various in vivo observations are all exponential in form. Further information concerning the disposal and distribution of radiothyroxine may be inferred by analyzing such curves in a manner similar to that used for the study of inorganic radioiodide (4, 7, 8, 9).

The curve of total radioactivity in urine can be fitted with a function of the form

$$Q_u = Q_u f(1 - e^{-rt})$$

where Q_u is the amount of radioiodine, expressed as percentage of dose, excreted in any time, t, following injection; $Q_u f$ is the asymptotic ($t = \infty$ infinity) value of the function Q_u, and r is a rate constant. Similarly the various in vivo observations may be fitted with a function of the form

$$Q_e = Q_e o e^{r' t}$$

where Q_e is the quantity of radioactivity in counts per second at time t, $Q_e o$ is the value of the function corresponding to $t = 0$, and r' is the rate constant.

The parameters $Q_u f$ and r for the urine curve are evaluated by the method previously described, consisting in plotting log $(Q_u f - Q_u)$ against t for various estimated values of $Q_u f$ until the relationship fits a straight line and from the slope of this line evaluating r. In the case of the various in vivo observations, the parameters $Q_e o$ and r' are evaluated from a straight line fitted to the plot of log Q_e against t.

The curve of precipitable radioactivity in blood fits a double exponential function similar to that employed by Dominguez, Corcoran and Page (10) in the case of intravenously administered mannitol:

$$C = C_a e^{-\alpha t} + C_b e^{-\beta t}$$

where C is the concentration of precipitable radioactivity in serum at any time, t, expressed as percentage of dose per liter of serum, C_a and C_b are the values of the respective functions corresponding to $t = 0$, and α and β are the respective rate constants. The parameters C_b and β are first evaluated from a straight line fitted to the plot of log C against t. The antilogarithms of the extrapolated points on this line are subtracted from the observed values of C on the initial portion of the curve (which do not fit the line) and the logarithms of the differences are plotted against time as a separate curve. The parameters C_a and α are evaluated from a straight line fitted to the plot of this latter curve. The sum of C_a and C_b may be taken to be the theoretical or extrapolated value of C corresponding to $t = 0$. In order to obtain values for comparison, the curve of total radioactivity in blood can be treated in the same manner. The various curves obtained after intravenous administration of thyroxine, plotted in the manner just described, are shown in Figure 3 (*a* and *b*).

The values obtained from analysis of the blood curves (Table 1) provide quantitative information about the several metabolic events which occur: 1. There is an immediate distribution of thyroxine in the plasma, since the initial volume[1] of distribution is 48 cc. per kilogram of body weight. This

[1] Volume of distribution is here defined as the volume which would be occupied by the material in the organism assuming a concentration uniformly the same as that observed in serum.

value corresponds fairly closely to the normal range of plasma volume. 2. There is immediately a rapid exponential decrease of radioactivity in the blood for a period of approximately six hours. This apparently represents diffusion out of the plasma into a larger volume of distribution (11.1 liters = 193 cc. per kilogram of body weight). Perhaps fortuitously, this second volume of distribution has approximately the dimensions of extracellular fluid, and is smaller than the volume of distribution of inorganic iodide. 3. After six hours there becomes evident a secondary, exceedingly slow exponential disappearance of radioactivity from this larger, second compartment, presumably largely or entirely into feces and urine. 4. Accompanying the disappearance of precipitable radioactivity, there appears a small inorganic iodide fraction in serum. The magnitude of the inorganic iodide fraction is so small as to preclude any kinetic evaluation because of the inaccuracy of the observations, owing to errors of occlusion and counting.

The rate of disappearance of radiothyroxine from blood once equilibrium is reached is quite slow, 0.76 per cent per hour, corresponding to a half

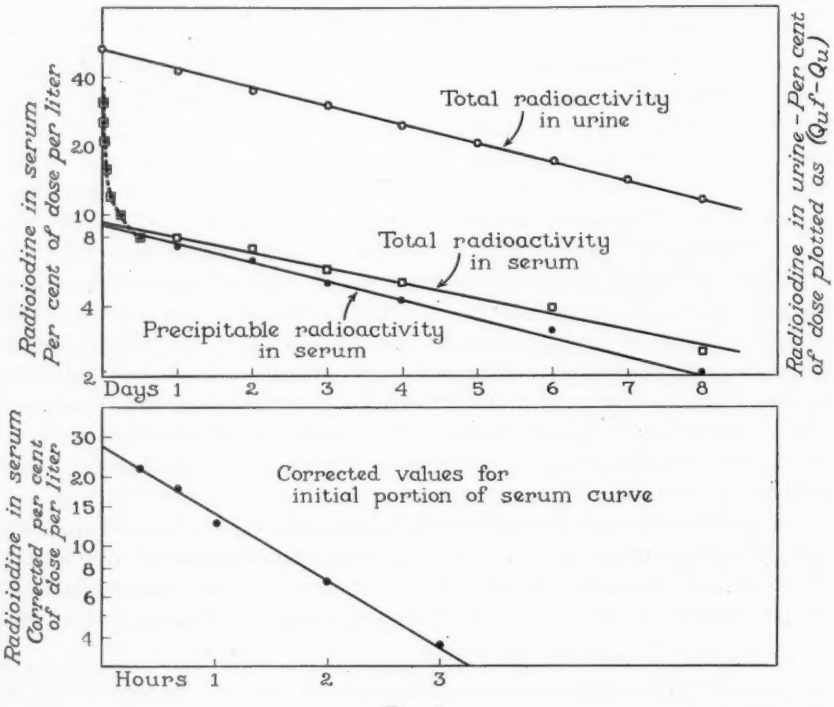


FIG. 3*a*

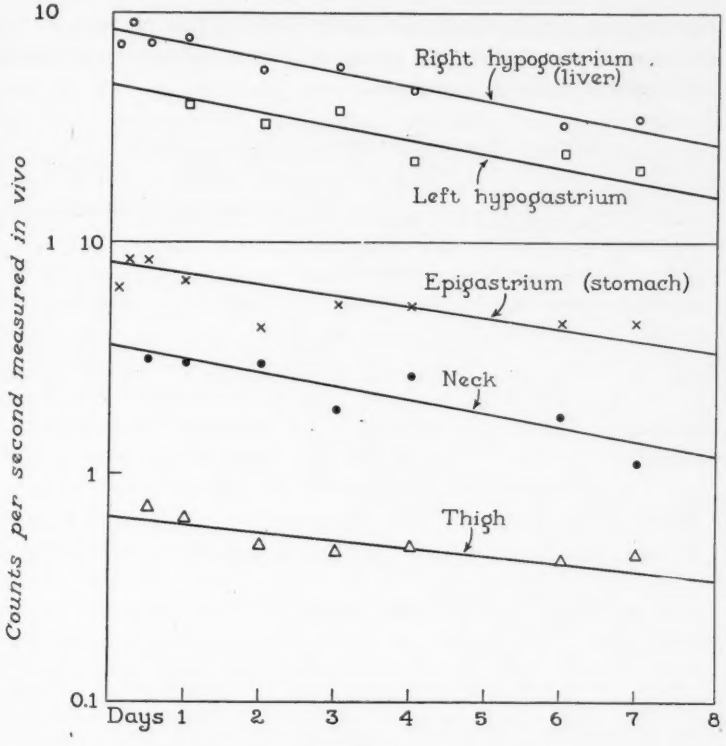


FIG. 3*b*

FIG. 3. Semilogarithmic plots of curves after intravenous administration of radiothyroxine. The methods of plotting the curves are given in the text. *a*. Comparison of blood and urine curves. The urine curve parallels (that is, has the same rate as) the curve of precipitable radioactivity in serum. The process of initial diffusion of thyroxine out of the plasma can be evaluated from the first portion of the blood curve, which may be plotted separately for this purpose, as shown in the lower panel of *a*. *b*. Comparison of in vivo curves. The slopes all correspond fairly closely to that of the curve of *total* radioactivity in serum.

value time of 3.8 days in this patient. This is about one tenth of the rate of disappearance of inorganic iodide in the same patient, which is 7.6 per cent per hour, corresponding to a half value time of 9.1 hours. In contrast to this, the diffusion of thyroxine out of the plasma space (69 per cent per hour; half value time, 1.0 hour), although rapid in comparison with its subsequent disappearance, is slow enough to be measured with ease and quite slow compared with the great speed at which electrolytes, including inorganic iodide, diffuse out of the blood. The observations on the blood

after intravenous administration of radioiodide in this patient, of course, show no trace of the equilibrium phase, which must have been completed within a comparatively few minutes.

TABLE 1. VALUES DERIVED FROM SERUM CURVES

	Initial concentration (*Co*), per cent of dose per serum	Rate constants, per cent per hour	Volume of distribution		
			basis	liters	cc. per kilogram
Radioiodide	6.2	$r = 7.6$	$mm(1/Co) =$	16.2	271
Radiothyroxine (precipitable)	36.0	$\alpha = 69.0$* $\beta = 0.76$	$(1/Co) =$ $(1/C_b) =$	2.8 11.1	48 193
(Total)	*	$\beta = 0.60$	—	—	—

* During the initial limb of the curve precipitable radioactivity = total radioactivity.

TABLE 2. VALUES DERIVED FROM URINARY CURVES

	Renal fraction ($Q_u f$), per cent of dose	Disappearance rate (r), per cent per hour	Renal excretion ($Q_u f \times r$), per cent per hour	Extrarenal disposal [$r(1-Q_u f)$], per cent per hour
Radioiodide	83.5	6.2	5.2	1.0
Radiothyroxine	53.0	0.81	0.43	0.38

The curve of excretion of radioiodine in urine (Table 2) after intravenous administration of radiothyroxine levels off at a rate which, within the limits of experimental error, is the same as the rate of disappearance of organic radioiodine from blood. The tentative conclusion might therefore be drawn that the radioiodine in urine is directly derived from the organic fraction in blood, and that the same kinetic relations hold between urinary excretion and blood concentration as have previously been described for inorganic iodide. It is of particular interest to note, however, that the greater part (85 per cent) of the radioiodine appearing in urine after intravenous injection of radiothyroxine is in the form of inorganic iodide. The capacity of the patient's kidneys to excrete inorganic radioiodide has been shown to be much greater than the rate at which radioiodide is appearing in the urine

after administration of radiothyroxine (renal excretion rate 5.2 per cent per hour after administration of radioiodide; 0.43 per cent per hour after administration of radiothyroxine and in the latter instance not all represents iodide). The rate at which radioiodine appears in the urine after administration of radiothyroxine is therefore not, as it is after administration of radioiodide, a contributory factor to the rate of disappearance of the material from the blood. Instead the reverse must be assumed; namely, that the rate of renal excretion of radioiodine in this instance reflects the rate of catabolic breakdown of radiothyroxine, plus perhaps direct loss of hormone in the feces, if that occurs. The fact that in addition to its being the principal urinary product, a measurable, though small, fraction of inorganic radioiodide is built up in the blood over a period of time, is further evidence that factors governing the disappearance of thyroxine from the blood are probably independent of renal excretion as such. This does not exclude the possibility of course that the renal parenchyma could prove to be an important site of such catabolic breakdown.

The curves constructed from in vivo observations over the neck, thigh, stomach, liver and left hypogastrium (Table 3) also form perfectly satisfactory exponential decay curves. It is interesting to note, and perhaps significant, that the rates of disappearance of radioactivity from these sites are consistently less than those described previously in urine and organic iodine in blood. The average of the five rates obtained for radiothyroxine is 0.55 per cent per hour, which corresponds to a half value time of 5.3 days. This more nearly corresponds to the half value time for *total* serum radioactivity (4.8 days) than to that for organic serum radioactivity (3.8 days). This may be entirely reasonable, since the inorganic iodide fraction being built up gradually in the blood and body fluids would prevent the organs measured in vivo from reflecting accurately the disappearance rate of organic material per se.

The measurements of initial concentration over the neck and the thigh are of approximately the same magnitude as those over these areas after administration of inorganic radioiodide. Those over the stomach (epigastrium) and liver (right hypogastrium) are nearly twice as great. Both these values are taken to reflect radioactivity largely in the liver, a fact which receives support from the much lower values consistently observed in the left hypogastrium. Furthermore, the radioactivity in the epigastrium and right hypogastrium initially was not very much larger than after administration of iodide, but increased for a period of approximately six hours, a fact which appears to coincide nicely with the initial, or equilibrium, phase of the blood curve. The liver is apparently one region into which thyroxine diffuses from its original plasma compartment. In vivo methods are, unfortunately, incapable of providing any quantitative

TABLE 3. VALUES DERIVED FROM IN VIVO CURVES

Form of radioiodine administered	Site	Initial concentration, counts per second per 100 microcuries	Disappearance rate, per cent per hour
Radioiodide	Neck	3.1	5.3
	Thigh	1.2	7.3
	Stomach (epigastrium)	4.6	6.0
	Liver (right hypogastrium)	4.4	6.9
	Mean	—	6.4
	(Urine)	—	6.2
	(Total blood)	—	7.6
Radiothyroxine	Neck	3.6	0.56
	Thigh	0.8	0.58
	Stomach (epigastrium)	8.0	0.48
	Liver (right hypogastrium)	8.4	0.60
	Left hypogastrium	4.8	0.55
	Mean	—	0.55
	(Urine)	—	0.81
	(Total blood)		0.60
	(Precipitable blood fraction)	—	0.76

or absolute measure of the amount of radioiodine in such an extended source as the liver. Considering the remarkably small space in which thyroxine is finally distributed in the body (11.1 liters = 193 cc. per kilogram), quantitative evaluation of the magnitude of the "thyroxine space" in the liver becomes exceedingly important. An important inference which must be drawn from the small dimensions of the "thyroxine space" of the body

is that if thyroxine diffuses into muscle, as it almost surely must, there must exist a gradient of considerable magnitude between plasma thyroxine concentration and muscle thyroxine concentration.

We have attempted in Table 4 an accounting of the quantitative distri-

TABLE 4. DISTRIBUTION OF A DOSE OF RADIOTHYROXINE EIGHT DAYS AFTER INTRAVENOUS INJECTION

Site	Per cent of dose
Excreted in urine	41.3
Excreted in feces	11.5
Distributed as organic iodine*	23.3
Distributed as inorganic iodine†	8.1
Unaccounted for	15.8
Total	100.0

* Calculated from the concentration of precipitable radioactivity in serum, as per cent of dose per liter, multiplied by the volume of distribution of precipitable radioactivity ($2.1 \times 11.1 = 23.3$).

† Calculated from the concentration of nonprecipitable radioactivity in serum, as per cent of dose per liter, multiplied by the volume of distribution of inorganic radioiodine as determined from the control study with labeled inorganic iodine ($0.5 \times 16.2 = 8.1$).

bution of the dose of radiothyroxine as a whole at the end of the period of observation; namely, eight days. The quantity recovered in urine and in feces, that calculated as remaining in the body in "thyroxine space" and that remaining in the body in "iodide space" total 84.2 per cent of the dose, leaving 15.8 per cent unaccounted for. This residue undoubtedly reflects any errors in measurement or analysis, and in particular any errors in collections, including any fecal material not yet evacuated. The data do not exclude the possibility that there might be a very small fraction of iodine which became fixed in tissue and remained there for a much longer period, so as to escape observation with the methods employed in and during the time of this experiment.

INTERPRETATION

To the extent that data obtained with labeled racemic thyroxine in athyreotic subjects can be applied to natural thyroxine in the normal

subject, our observations on the metabolism of thyroxine after oral and intravenous administration can be marshaled to indicate a highly tentative picture of the metabolism of thyroid hormone under normal conditions. On entry into the circulation, thyroxine is confined at first to the plasma, from which it is transferred to the tissues of the body, including especially such organs as the liver, and becomes equilibrated with the thyroid hormone already present in tissue. In the tissues thyroid hormone is catabolized mainly to iodide and to a minor extent is split apparently at its ether linkage. The iodide liberated becomes equilibrated with serum iodide, and is present as only a small percentage of the total serum iodine, partly because it is disposed of rapidly and partly because its volume of distribution is comparatively large. The liberated iodide present in blood is eliminated mainly in the urine. Thyroid hormone is not accumulated by the thyroid and reutilized. Iodide liberated in the catabolism of thyroid hormone is reaccumulated and reutilized in a normal person. Approximately 20 per cent of the liberated iodide would be accumulated by the normal thyroid. The iodide of dietary origin probably accounts for far more of the iodide utilized by the normal thyroid for synthesis of new thyroid hormone than does the small proportion of iodide liberated from the catabolism of thyroid hormone which is reaccumulated.

The bulk of thyroid hormone is therefore deiodinated and excreted in the urine as iodide. A small, almost negligible amount of thyroid hormone appears to be excreted unchanged, and another small portion as a split product, similar in behavior to diiodotyrosine. Perhaps as much as a third or more of the thyroid hormone is excreted in the feces in protein-bound form, but the chemical nature of the fecal iodine is uncertain. Thus, the economy of the organism for the conservation of iodine from thyroid hormone is relatively poor.

SUMMARY

The metabolic behavior of racemic radiothyroxine administered intravenously was studied in a myxedematous patient, maintained at an euthyroid level with racemic nonlabeled thyroxine. After one half-life of the thyroxine I^{131}, 41 per cent of the radioactivity was excreted in the urine and 12 per cent in the feces. Eighty-five per cent of the urinary I^{131} was present as inorganic iodide and 15 per cent as organic I^{131}, consisting of both thyroxine and diiodotyrosine. This pattern was essentially like that obtained in a similar study in which radiothyroxine was administered orally. Various aspects of the kinetic behavior of radiothyroxine are described.

REFERENCES

1. HAMILTON, C. F.; ALBERT, A.; POWER, M. H.; HAINES, S. F., and KEATING, F. R., JR.: The action of iodocasein on human myxedema, with comparative studies on the fate and distribution of synthetic radioactive iodocasein and of I^{131} during hypothyroidism and euthyroidism, (Abstr.), *J. Clin. Investigation.* **27**: 539 (July) 1948.
2. HAMILTON, C. F.; ALBERT, A.; POWER, M. H.; HAINES, S. F., and KEATING, F. R., JR.: The behavior of labeled iodocasein in human myxedema, *J. Clin. Endocrinol.* **9**: 828–840 (Sept.) 1949.
3. ALBERT, A.; RALL, J. E.; KEATING, F. R., JR.; POWER, M. H., and WILLIAMS, M. M. D.: The behavior of labeled thyroglobulin and labeled thyroxine in patients with myxedema, *J. Clin. Endocrinol.* **9**: 1392–1405 (Dec.) 1949.
4. KEATING, F. R., JR., and ALBERT, A.: The metabolism of iodine in man as disclosed with the use of radioiodine, *Recent Progress in Hormone Research*, Academic Press (in press).
5. TAUROG, ALVIN, and CHAIKOFF, I. L.: The nature of the circulating thyroid hormone, *J. Biol. Chem.* **176**: 639–656 (Nov.) 1948.
6. LEBLOND, C. P., and GROSS, J.: The mechanism of the secretion of thyroid hormone, *J. Clin. Endocrinol.* **9**: 149–157 (Feb.) 1949.
7. KEATING, F. R., JR.; POWER, M. H.; BERKSON, JOSEPH, and HAINES, S. F.: The urinary excretion of radioiodine in various thyroid states, *J. Clin. Investigation.* **26**: 1138–1151 (Nov.) 1947.
8. MCCONAHEY, W. M.; KEATING, F. R., JR., and POWER, M. H.: The behavior of radioiodine in the blood, *J. Clin. Investigation.* **28**: 191–198 (Mar.) 1949.
9. LUELLEN, T. J.; KEATING, F. R., JR.; WILLIAMS, M.M.D.; BERKSON, JOSEPH; POWER, M. H., and MCCONAHEY, W. M.: Relative measurement in vivo of accumulation of radioiodine by the human thyroid gland: comparison with radioactivity in peripheral tissues, *J. Clin. Investigation.* **28**: 207–216 (Mar.) 1949.
10. DOMINGUEZ, RAFAEL; CORCORAN, A. C., and PAGE, I. H.: Mannitol: kinetics of distribution, excretion, and utilization in human beings, *J. Lab. & Clin. Med.* **32** (pt. 2): 1192–1202, 1947.

SURGICAL TREATMENT OF CARCINOMA OF THE THYROID GLAND*

B. MARDEN BLACK, M.D.

From the Division of Surgery, Mayo Clinic, Rochester, Minnesota

ATTEMPTS to devise a standardized surgical procedure for managing carcinoma of the thyroid gland have not been signally successful, chiefly because of the marked differences in biologic behavior of the different types of carcinoma. Thus, a procedure that is rational for the management of papillary lesions is irrational for the treatment of malignant adenomas and diffuse adenocarcinomas. Removal of thyroid, contiguous tissues and zones of venous and lymphatic spread is an impossibility because of neighboring vital structures; and the necessity of radical operation in the majority of cases has been challenged. Survival and recurrence rates have been disappointing in the evaluation of the procedures which have been proposed, partly because of the slow natural progress of lower grades of malignancy and partly because of extremely rapid progress of more malignant lesions. In addition, because of differences in fundamental criteria of malignancy adopted by different pathologists, results following treatment at different institutions may not be comparable.

At the Mayo Clinic, the extent of the surgical procedure is determined by the type of malignancy and its local spread, and no effort is made to manage all such growths in the same fashion. Radical operations are rarely carried out, except in the case of the papillary form, and even lesions of this type are usually treated by limited resections. This approach to the problem implies a knowledge of the type of malignancy, which can be secured only by biopsy (1); and information as to its local extent, which requires exposure and mobilization of the thyroid, at least in cases in which there is a reasonable chance of cure. The treatment of the primary lesion and that of the surrounding tissues will be discussed separately. This departure from the usual method of discussing treatment according to type of carcinoma was chosen in order to bring the discussion into line with actual practice, since the thyroid gland is managed first, and regional tissues are considered only after the primary lesion has been dealt with.

Received for publication June 11, 1949.

* Read at the Annual Meeting of the American Goiter Association, Madison, Wisconsin, May 27, 1949.

This article will be included in the bound volume of the "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for sale early in 1950.

TREATMENT OF PRIMARY LESION

Carcinoma limited to one lobe.—The carcinomas of the thyroid with the most favorable prognosis from the standpoint of local spread, are small infiltrating lesions of lower grade, particularly papillary growths, and well-encapsulated malignant adenomas. In either case, since neither the capsule of the gland nor the capsule of the adenoma has been transgressed by the carcinoma, the diagnosis virtually can never be made with certainty clinically, and is usually made only on microscopic examination of tissue removed at subtotal lobectomy. Although wide local excision is probably adequate to deal with such growths, some uncertainty almost always exists as to whether the primary lesion has been completely removed. By the time the diagnosis has been established, the surgeon has usually ligated bleeding points and sutured the remnant, so that examination of the remnant for the presence of unremoved carcinoma is usually not satisfactory. Similarly, the removal of blocks of tissue by the pathologist for microscopic examination has so changed the surgical specimen that the relationship of the carcinoma to the resected edge of the tissue is not apparent. In such cases, total lobectomy only will remove all uncertainty, and if the incision is still open, I believe this should be carried out. Total removal of the lobe obviously precludes recurrence within the remnant and equally obviously removes all regions of multicentric carcinoma in the lobe.

If the pathologist's diagnosis of malignancy is not available until after the incision has been closed, and particularly if the correct diagnosis is delayed for several days, the incision is usually not reopened for removal of the remnant, and uncertainty as to the adequacy of removal remains until time proves or disproves the presence of carcinoma in the remnant. The difficulty of pathologic diagnosis of many cases of carcinoma of the thyroid needs no elaboration, but if the correct diagnosis is not made at a time when the surgical procedure can be extended, occasional patients will continue to be treated inadequately, and local recurrences in the remnants will continue to develop.

The inadequacy of subtotal lobectomy in the management of even papillary lesions was well demonstrated by the results following treatment in a series of 112 cases of papillary adenocarcinomas recently reported by me (2). Among 36 cases in which subtotal lobectomy had been carried out, there was recurrence in the remnant in 4. Conversely, total lobectomy in 23 cases was not followed by any local recurrences in the region that had been occupied by the lobe. It is probable that the local recurrence rate of more malignant, infiltrating lesions is far higher.

Carcinoma involving both lobes.—When both lobes of the thyroid are involved, consistency and logic would seem to demand total thyroidec-

tomy. However, in actual practice the procedure is rarely indicated. In most cases one lobe is affected far less than the other, and a reasonably radical removal of the carcinoma can be achieved by removing totally the lobe on the more involved side and by preserving a small remnant of the less affected lobe (3). In many such cases, the presence of metastatic growths or involvement of the capsule of the thyroid and surrounding structures makes the lesion so doubtfully operable that the possibility of recurrence in the remnant is of relatively little importance. An occasional papillary adenocarcinoma will involve the entire thyroid gland without metastasizing beyond the cervical lymph nodes or infiltrating beyond the capsule of the thyroid. There were 2 such cases among the 112 cases of papillary adenocarcinoma previously mentioned. In both cases, total thyroidectomy was carried out.

Carcinoma infiltrated beyond capsule of the thyroid.—In the absence of distant metastatic growths, operability of carcinoma of the thyroid depends on the extent of local invasion beyond the capsule of the gland, and fixation of the thyroid is often the most important consideration in determining operability (3, 4). When the thyroid has become fixed by carcinomatous infiltration of surrounding structures, the patient should not be operated on, since expected benefit is not commensurate with risk (3). Occasionally, fixation of the carcinomatous thyroid is not due to invasion of surrounding structures but to mere wedging of the goiter in the superior strait of the thorax, and this possibility should be considered before one refuses surgical exploration in such cases. If some mobility still remains, suggesting that invasion has occurred in a limited region, surgical exploration is indicated, since the carcinoma may be removable completely or possibly may be removable except for small masses which can be treated by the local application of radium or radon seeds. However, in any case in which carcinoma has actually invaded surrounding structures, except for the infrahyoid muscles and possibly the sternocleidomastoid muscle, the chance of cure is remote.

TREATMENT OF REGION OF LYMPHATIC AND VASCULAR SPREAD

The view has been expressed previously by Pemberton (3) that radical removal of contiguous tissue, except in the case of papillary adenocarcinoma, is rarely indicated in the treatment of carcinoma of the thyroid gland. This view is based on the fact that malignant adenomas and diffuse adenocarcinomas almost invariably prove inoperable by the time sufficient spread has occurred to involve adjacent structures. Rarely, in the case of malignant adenomas, local permeation through the veins of the thyroid, even to the internal jugular vein, is found. In such cases, providing the lesion is otherwise operable, radical removal of thrombosed veins is feasible

and indicated (5, 6, 7, 8). In the absence of thrombosis of veins it is debatable whether survival rates could be improved by radical removal of veins free from evident malignant extension or thrombosis.

Lymphatic spread of malignant adenomas virtually never occurs as long as the malignant lesion remains within the capsule of the adenoma and is rare until the capsule of the thyroid gland has been invaded (3, 5) In practice, involvement of nodes is such a late event that the lesion is usually otherwise inoperable by the time the nodes become involved. Conversely, nodes are involved so late in the course of malignant adenomas that so-called prophylactic removal does not seem warranted. In the case of diffuse adenocarcinomas, it has long been agreed that by the time either intravascular propagation or lymphatic spread has occurred the lesion is generally incurable, and that radical removal of contiguous tissues is a hopeless gesture. Unless the primary lesion is small and confined to one lobe, survival rates following the removal of lesions of this type are so poor, regardless of the magnitude of the operation, that there is little hope of improving results by extending present known methods of treatment.

If such reasoning is acceptable, the question of radical removal of regional tissues pertains, for practical purposes, to papillary adenocarcinomas. That lesions of this type may remain confined to the thyroid for years, that they may involve many or few regional lymph nodes, that spread beyond the capsule of an involved node is delayed and unusual, are generally accepted conclusions which obviously have important bearing on surgical management. Data pertaining to 112 consecutive cases of papillary adenocarcinoma recently reviewed by me (2) will be used subsequently in discussing the management of such lesions. Of the 112 cases, 18 were found inoperable, most commonly because of local invasion but occasionally because of distant metastatic growths, whereas 94 were operable technically in that all gross carcinoma could be removed. Lymph nodes were involved in 44 cases in the series, but there was no involvement in 68 cases.

In the absence of evident metastases to lymph nodes, I do not believe that lymphatic structures should be disturbed. In the majority of cases lymph nodes never become involved (68 of 112 cases), but when such metastases do occur, the affected nodes are usually grossly evident on clinical examination or at the time of thyroidectomy. So-called prophylactic dissections of lymphatic structures do not seem warranted since the metastatic deposits remain confined to the node for prolonged intervals, and virtually never extend so far locally that the node cannot be removed. In only 9 of the 18 inoperable cases were nodes affected, and in none of the 9 cases with nodal involvement was the case judged inoperable because of fixation of cervical metastatic growths.

If lymph node metastasis is not apparent clinically, rather specific attention should be paid to certain groups of nodes at the time the thyroid gland is explored, since in cases without massive involvement of nodes, spread is more or less predictable (2). Bilateral spread does not occur unless the isthmus is involved and, consequently, with well-lateralized lesions, attention can be limited to the side of the lesion. Lesions near the superior pole spread particularly to the lower nodes of the upper deep jugular group, whereas those deep within the lobe are more likely to spread to the lower deep jugular nodes and those near the inferior pole spread to anterosuperior mediastinal nodes. Most careful attention should be given to nodes in the immediate vicinity of the thyroid and particularly along the tracheo-esophageal groove. Nodes in this region were involved in 69 per cent of 44 cases in which any nodal involvement had occurred. Since in many cases total lobectomy will have been carried out and the recurrent laryngeal nerve will have been exposed throughout the operative field, involved nodes are apparent and easily removed. The region requires special consideration, since scarring after lobectomy will prevent satisfactory subsequent dissection.

In cases in which nodes have become involved, extensive cervical dissections have been recommended, even to the extent of excising lymphatic tissue from clavicle to mastoid process and sacrificing the internal jugular vein and sternocleidomastoid muscle (9, 10). Such extensive dissections are rarely thought advisable at the clinic, since it has been found that papillary adenocarcinomas can be satisfactorily managed by more limited excisions. If all cases of papillary adenocarcinoma of the thyroid in which there is lymph node metastasis are considered, extensive involvement of nodes is by no means the rule. Of 44 cases with nodal involvement one or at most a few nodes were affected in 28 cases, whereas many nodes in several anatomic groups were involved in 16 or in only slightly more than one third of the cases. Extensive removal of lymphatic tissues is carried out at the earliest possible occasion presumably in an effort to prevent involved nodes from becoming inoperable. Among the 44 cases, in the vast majority of which limited dissection was performed, none was found inoperable or became inoperable solely because involved cervical nodes could not be removed.

Discussion of cosmetic results is manifestly inappropriate if a superior cosmetic result can be achieved only at the cost of failure to cure the patient. However, with papillary lesions, such considerations are timely since results after limited dissections are presumably no worse than those after extensive cervical dissections, and since the patients with extensive involvement of nodes are sufficiently young to make such considerations important. The patients in the present series, with extensive cervical

metastatic growths, had a mean age of 25.9 years; two thirds were less than 30 years, and one third less than 20 years of age.

In general, I believe that removal of the anatomic group or groups of nodes in which a metastatic growth has developed is sufficiently radical. The 44 cases with involved nodes were managed for the most part in this manner. In 9 cases the lesion was found hopelessly inoperable, leaving 35 patients for appraisal. No further removal of lymph nodes became necessary in 26 patients, but lymph nodes became clinically evident subsequent to the original operation in 9. In 4 of the 9, however, local recurrence in the remnant of the thyroid was present when the nodes appeared. In none of the 9 cases were the cervical nodes which appeared subsequently found inoperable. In the majority of cases the nodes appeared in a previously undissected region and presented no particular problem in removal.

OPERATIVE PROCEDURE

Whether carcinoma is suspected or not, the usual incision for operations on the thyroid gland is used. The diagnosis of carcinoma is established by biopsy or, in many cases, by microscopic study of tissue resected at subtotal lobectomy. If the carcinoma is clinically significant, and if the lesion is recognized as malignant before the incision is closed, the affected lobe is removed totally. In more advanced cases, when the malignant growth has invaded surrounding structures, particularly in the case of papillary lesions and malignant adenomas, a determined effort is made to remove as much of the carcinoma as possible, leaving only nonremovable carcinomatous tissue behind. The recurrent laryngeal nerve is usually preserved unless it is actually involved. If the nerve is involved it may be removed on one side. If the carcinoma has extended beyond the capsule posteriorly or if tracheo-esophageal nodes are involved, preservation of parathyroids should not be attempted. It is usually possible, however, to avoid total parathyroidectomy. In still more advanced cases, an attempt is made to expose the trachea in anticipation of ultimate tracheotomy.

If the lesion is a papillary adenocarcinoma and lymph nodes are involved in the lower deep jugular region, which is most usual, the incision is extended proximally along the posterior border of the sternocleidomastoid muscle on the side of the involvement, and the nodes and node-bearing fascia of the lower deep jugular region are removed, the deep jugular vein and sternocleidomastoid muscle being preserved. If upper deep jugular nodes are involved, they are removed as a group through a second incision, made parallel to a skin fold in the upper cervical region. If nodes are involved bilaterally, a similar procedure is carried out on the opposite side, usually about three months later. In such cases, if bilateral total lobectomy is necessary to remove all of the primary lesion, the second

lobe is removed at the second operation. If subtotal removal of the second lobe is judged adequate, this is carried out at the same time as removal of the first lobe, the necessity of re-exposure of the thyroid gland thereby being avoided.

Particularly in the case of malignant adenomas, the thyroid veins are carefully examined for evidence of venous permeation. If the veins are found thrombosed the involved veins are resected, the incision being extended proximally along the posterior border of the sternocleidomastoid muscle to afford sufficient exposure. If there is no evidence of permeation, the veins are not resected. Extensive dissection for the removal of lymph nodes is not carried out, although limited removal of involved nodes is indicated occasionally.

In cases in which extensive removal of nodes is anticipated, intratracheal anesthesia is necessary since the operation is too extensive for the usual local field block augmented by nitrous oxide. This is a further factor limiting the operation to one side of the neck (7).

REFERENCES

1. Broders, A. C.: Surgical pathology of the thyroid gland, *West. J. Surg.* **48**: 620–632 (Oct.) 1940.
2. Black, B. M.: Papillary adenocarcinoma of the thyroid gland: so-called lateral aberrant thyroid tumors, *West. J. Surg.* **56**: 134–144 (Mar.) 1948.
3. Pemberton, J. deJ.: Malignant lesions of the thyroid gland: a review of 774 cases, *Surg., Gynec. & Obst.* **69**: 417–430 (Oct.) 1939.
4. Horn, R. C., Jr.; Welty, R. F.; Brooks, F. P.; Rhoads, J. E., and Pendergrass, E. P.: Carcinoma of the thyroid, *Ann. Surg.* **126**: 140–155 (Aug.) 1947.
5. Crile, G., and Crile, G., Jr.: Radical operation for malignant tumors of thyroid gland, *Surg., Gynec. & Obst.* **64**: 927–934 (May) 1937.
6. Gamble, H. A.: Carcinoma of the thyroid gland, *Tr. Am. A. Study Goiter.* pp. 343–347, 1939.
7. Ward, Robertson: Malignant goiter: lessons to be learned from a 20 year follow-up, *West. J. Surg.* **55**: 383–388 (July) 1947.
8. Welti, Henri, and Huguenin, Rene: Malignant tumors of the thyroid gland: a study of eighty-eight cases, *Tr. Am. A. Study Goiter.* pp. 141–153, 1938.
9. Cattell, R. B.: More optimistic approach to cancer of thyroid, *West. J. Surg.* **54**: 444–449 (Nov.) 1946.
10. Lahey, F. H.; Hare, H. F., and Warren, Shields: Carcinoma of the thyroid, *Ann. Surg.* **112**: 977–1005 (Dec.) 1940.

EDITORIAL

JOURNAL OF CLINICAL ENDOCRINOLOGY

Managing Editor: WILLARD O. THOMPSON
Publication Committee: WARREN O. NELSON, ROY G. HOSKINS, E. PERRY MCCULLAGH
Editorial Board: Willard M. Allen, C. L. Buxton, Ray Farquharson, Thomas F. Gallagher, Samuel F. Haines, Roy G. Hoskins, John E. Howard, Laurance W. Kinsell, Francis D. W. Lukens, H. L. Mason, Samuel Soskin, George Thorn, Lawson Wilkins.

THE THYROID-PITUITARY APPARATUS AS A SERVO (FEED-BACK) MECHANISM

OF RECENT years communications and control engineers have increasingly emphasized the concept of "servo mechanisms" in dealing with "automatically" controlled devices (1). A servo system is defined as one in which variations or consequences of variations in the quantity of the output of an apparatus are "fed back" for the control of the system. The thermostat which regulates the furnace in a heating system of a residence affords a simple example of such feedback mechanisms. When the room temperature that surrounds the thermostat falls below the level at which it is "set," a device is activated whereby the furnace is turned on; then when the temperature rises above a determined critical level, the furnace is turned off. A much more complicated example of a servo mechanism is that employed in the radar aiming of a large gun on a rolling, advancing battleship. This control is brought about by a complicated group of devices whereby the position of the gun is rapidly and continuously kept in match with the position of an aiming device that an observer holds trained on the target. Further corrections for wind deflection and target distance are also fed into the system. Thus, a few pounds of human muscle, itself regulated by nervous feed-back impulses, can keep a two-hundred-ton mechanism in continuous, accurate adjustment to its function.

Recently Wiener (2) has pointed out that many physiologic processes are regulated by feed-back control and has suggested that much clarification and insight may be gained by the application of servo theory to such functions.

The pituitary-thyroid axis affords an example, *par excellence,* of a physiologic servo mechanism. When the titer of circulating thyroxine rises, the anterior pituitary is selectively inhibited and the discharge of thyrotropin is thereby decreased. Contrariwise, episodic or persistent thyroxine deficiency, if sufficient in degree, results in augmented thyro-

tropin production with resulting tendency for the production of more thyroid hormone. The two questions that arise at once, when an application of servo theory to the pituitary-thyroid apparatus is made, are: a) the quantitative relationships between the blood-thyroxine titer and thyrotropin discharge and, b) the nature and control of the "setting" of the pituitary governor.

To consider the second problem first, the determining factor in the "setting" is, no doubt, the degree of reactivity of the pituitary cells to the thyroid hormone. If the responsivity is sluggish, a discharge point will obviously be reached only when the change in thyroxine titer is relatively great. On the other hand, a hypersensitive pituitary will respond to smaller changes in the titer. By this relationship it would seem possible to bring about a condition of either relative hypothyroidism or hyperthyroidism, depending merely on the "set" of the pituitary "hormostat," just as a house can be kept either cool or warm by the setting of the thermostat. Correspondingly, therapeutic measures addressed to modification of pituitary responsivity would be one rational method of modifying these conditions. Perhaps, as a case in point, the response of the thyroid gland to a cold environment is brought about by such an induced change in pituitary reactivity.

An associated problem in this connection is what effect a persisting change of blood-thyroxine level, itself, might have on the setting of the "hormostat." Could an initially ineffective dosage be used to bring about an increase in the feed-back lag and thus permit a gradual rise in the circulating titer? Immediately bearing on this problem is the consideration that the thyroid hormone is both an anabolism-promoting and a catabolism-promoting agent, the latter influence mostly predominating in the higher dosage ranges. In view of the fact that thyrotropin discharge is probably a catabolic event, a particular possibility of adaptive utility of the smaller dosage is suggested. It might set up a prolonged anabolic predominance in the anterior pituitary and thus raise the discharge threshold for thyrotropin to the point at which the feed-back mechanism would be correspondingly inoperative. Thus a low titer of thyroxine might be built up to a physiologically effective level. On teleologic grounds this surmise is attractive.

Problems of "setting," aside—is the feed-back control continuously and delicately active, as in case of the gun-aiming mechanism, or is there a sensible threshold factor as in case of the thermostat? (The ordinary home thermostat set at 68° goes "off" at about 70° and "on" at about 66°). This question has immediate relevance in the clinical use of thyroid substance as a drug. It is theoretically possible that as the titer of circulating thyroxine is increased, there is no response in the pituitary until a

certain threshold increment is experienced—which is to say that the feed-back functions only with a sensible lag. Evidence currently available would seem to favor the assumption that such is the case. Otherwise, in the presence of functioning thyroid gland tissue, administered thyroid substance would be a completely self-antidoting drug throughout the entire range at which the pituitary inhibiting mechanism is operative and up to the level at which thyrotropin production is entirely "paralyzed" Above that level, but only above that level, would conventional dosage-response relationships be expected to prevail.

The factor of lag as well as that of "setting" may be of particular moment as regards dosage levels at the lower end of the scale. Basing their conviction mostly on observations on the effects of thyroid administered in the higher dosage ranges, many clinicians are inhospitable to suggestions that the lower dosage ranges are of any utility. Granted that a sufficient lag in feed-back control normally exists, it might well be possible as a matter of basic physiology that by low dosages the circulating thyroxine could be increased and held persistently at a significantly higher level for an indefinite period. Indeed, a smaller dosage that does not activate the feed-back might be absolutely more effective than larger dosage that would bring the pituitary depressing mechanisms into play.

The foregoing discussion suggests a few angles of approach toward the application of servo theory to thyroid-pituitary physiology. Despite the fact that the thyroid gland has been an object of intensive study for nearly a century, our understanding of it is still inadequate. Some of the apparent paradoxes might be elucidated by further quantitative studies of the pituitary-thyroid relationships, such as the recent researches of de Robertis (3). Especially attractive would be more adequate knowledge of the different physiologic and pathologic factors that determine the "set" of the controlling apparatus—*i.e.*, the degree of responsivity of the pituitary to thyroid hormone—and ways of modifying this "set" in clinically desirable directions.

R. G. Hoskins

REFERENCES

1. James, H. M.; Nichols, N. B., and Phillips, R. S.: *Eds.*: Theory of Servomechanisms. New York, McGraw-Hill Co., 1947.
2. Wiener, N.: Cybernetics. New York, John Wiley and Sons, 1948.
3. de Robertis, E.: Assay of thyrotropic hormone in human blood, *J. Clin. Endocrinol.* **8**: 956–966 (Nov.) 1948.

Letters to the Editor

THYROTOXICOSIS FACTITIA

Follow-up on a case reported in *J. Clin. Endocrinol.* **8**: 532–543 (July) 1948
by Skanse, B. N. and Riggs, D. S.

TO THE EDITOR:

SKANSE and Riggs reported from the Thyroid Clinic of the Massachusetts General Hospital in the paper above cited, 2 cases of thyrotoxicosis factitia, 1 proven and 1 suspected.

I have now, thanks to the excellent cooperation of Dr. Jerome E. Cook of St. Louis, the proof in the latter case. This patient, Mrs. L. R. (No. 349932) was referred to me for study by Dr. Cook in April of 1942; again in January of 1947. On both occasions she was admitted to the Baker Memorial of the Massachusetts General Hospital. The history is given in the paper of Skanse and Riggs. The high spots are that she had had a subtotal thyroidectomy for supposed thyrotoxicosis in November of 1939. The thyroid tissue removed was reported to be normal, and there was no symptomatic improvement following operation. At the Massachusetts General Hospital in 1942 she had a moderate degree of hypermetabolism and an elevation of protein bound plasma iodine, but no goiter or eye signs. It was concluded that she might have residual thyrotoxicosis, but no one felt certain of this.

At the 1947 entry the clinical picture was unchanged. She had had courses of both iodine and thiouracil without benefit.

In the laboratory on this occasion we obtained basal metabolic rates in the plus thirties, plasma protein bound iodine 14.5 micrograms per cent (which is in the thyrotoxic range) and radioactive iodine excretion in forty-eight hours of 97 per cent of the administered dose (which is in the athyreotic range). This formula of elevated BMR and PBI and of subnormal RAI collection is, we believe, close to pathognomonic of thyrotoxicosis factitia. The ingested thyroid raises BMR and PBI, but causes disuse atrophy of the thyroid gland and thus depresses iodine collection to the vanishing point.

We accused Mrs. L. R. of this in 1947 but she hotly denied it and left the hospital. We reported our suspicions to Dr. Cook, and on September 14, 1949, he wrote us as follows:

"I have kept the patient under observation since you last saw her. Her status remained practically unchanged except for more persistent periods of auricular fibrillation, so that of the nine times on which I saw her from

January 7 to July 12 of this year, fibrillation was always present and the apex rate varied between 140 and 160. The various therapeutic agents previously tried were repeated with much the same negative results. In June she had an attack of acute appendicitis. Dr. J. Simon removed the appendix and she went through the incident much as a normal person would, without complication and without change in her previous clinical status.

"On September 3 her husband suffered an apoplectic stroke with coma. He was hospitalized and died on the third day. The wife remained at his bedside, was emotionally agitated, but I noted on the second day that her cardiac rate was slower than previously, whereas I had expected it might, under the circumstances, be at least at the usual maximum. I thought I might grasp at the chance for a decisive observation. I gave her large doses of sodium amytal, and when she was sufficiently dulled to be past objecting, I had her transferred to another hospital and ordered that no object or material of any sort be brought to her from her home. (She had not returned home since the first news of her husband's illness.)

"Her fibrillation ceased, the pulse rate came down rapidly. It was 52 yesterday morning. The electrocardiogram shows a normal mechanism and a BMR a few days ago showed a reading of 0. Meanwhile I had her home searched for evidence of medication. Yesterday her son brought me three large, identical bottles, each of which I would estimate could hold at least 500 tablets. Two of them were empty, but the third contained a liberal supply of light tan tablets stamped "P.D." which two pharmacists independently and without suggestion identified as one grain thyroid tablets of Parke, Davis. I have had no chance to make a physiological test of their identity, nor do I think it necessary.

"Mrs. R. has for the past ten days been under the observation of a psychiatrist and is to continue under his care pro tem. To date she has made no confession of thyroid medication, though she realizes that the change from her previous status is obvious to us. We have not put the direct question to her at this time; she was categorical in her denial when the question was put to her following her return from Boston in 1947."

The problem now is for the psychiatrist to discover why she did it.

Thyroid Clinic,
Massachusetts General Hospital,
Boston, Massachusetts.

J. H. Means, M.D.
Sept. 23, 1949

THE LOCAL ACTION OF TESTOSTERONE PROPIONATE ON THE DEVELOPMENT OF AXILLARY HAIR IN MAN

TO THE EDITOR:

IT IS a well established fact that the development of pubic and axillary hair is dependent upon androgens in men and upon estrogens in women. These substances may exert their influence either by indirect hormonal action or by acting directly upon the hair follicles. This problem has been set forth by Albright and co-workers (1) who observed very sparse axillary and pubic hair in a woman with Addison's disease who nevertheless menstruated regularly, which would indicate at least a sufficient estrogenic function. This fact, confirmed by similar observations

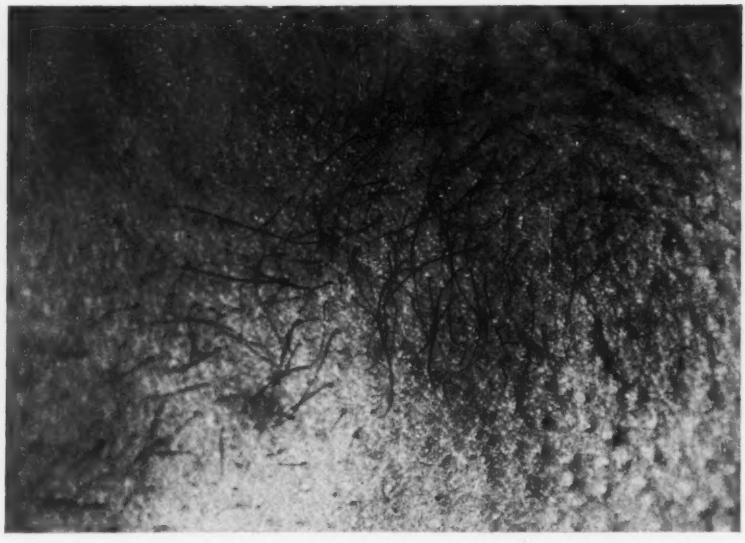


FIG. 1. Right axilla.

made by Kepler (2), and by Mussio Fournier and Proto (3), has made Albright and his associates think that development of axillary and pubic hair in women is not produced directly by the estrogens, but that the latter stimulate the secretion of some adrenal hormone (androgenic substance) which in turn causes development of female pubic and axillary hair.

In support of this hypothesis Albright and co-workers point out that in panhypopituitarism, in which there exists a marked hypofunction of the adrenal cortex, the administration of estrogens in women so affected does not produce development of axillary and pubic hair, whereas the latter re-

sult can be obtained in primary hypo-ovarianism because in this condition the cortical function is normal or only slightly diminished, as has been observed in the ovarian agenesis syndrome.

We now wish to report the case of a boy aged 13, in whom we used local applications of a hydro-alcoholic solution of testosterone propionate on the right axilla for about five months. This boy had very sparse pubic hair and no axillary hair. During the time of treatment the right axilla

FIG. 2. Left axilla.

was rubbed thrice weekly with the solution mentioned, while the left axilla was treated with the vehicle only. In each application 3.0 cc. of solution was employed containing some 10 mg. of testosterone propionate.

Under the influence of this treatment the penis was observed to grow slightly, there were more frequent erections, and muscular strength was greater. There was an increase in pubic hair, and an unequal growth of axillary hair, there being considerably greater development on the right side where the hormone solution had been applied, as can be seen in the photographs taken at the end of treatment (Figs. 1 and 2). This observation shows that androgens cause growth of axillary hair by direct action.

The Institute of Endocrinology,
Montevideo, Uruguay.

A. S. ALBRIEUX, M.D.
J. C. MUSSIO FOURNIER, M.D.
June 1, 1949.

REFERENCES

1. ALBRIGHT, F.; SMITH, P. H., and FRASER, R.: A syndrome characterized by primary ovarian insufficiency and decreased stature. Report of 11 cases with a digression on hormonal control of axillary and pubic hair, *Am. J. M. Sc.* **204**: 625, 1942.
2. KEPLER, E. J.; PETERS, G. A., and MASON, H. L.: Addison's disease associated with pubic and axillary alopecia and normal menses, *J. Clin. Endocrinol.* **3**: 497, 1943.
3. MUSSIO FOURNIER, J. C., and PROTO, A.: Un cas del maladie d'Addison avec absence de poils axillaires et pubiens malgré la conservation de la menstruation, *Bull. et. mém Soc. méd. d. hôp. de Paris* **63**: 62, 1947.

THE URINARY CORTICOSTEROID EXCRETION IN PRE-ECLAMPSIA AND ECLAMPSIA

TO THE EDITOR:

IN THE April issue of the *Journal of Clinical Endocrinology*, which arrived in Belgium about the middle of June 1949, there appeared an interesting paper by Louis Tobian, Jr. (1) concerning the "Cortical steroid excretion in edema of pregnancy, pre-eclampsia and essential hypertension."

It was thus by chance that we were informed of Tobian's results just when we were communicating to the Société d'Endocrinologie in Paris, our own results of studies on the same matter (2). Moreover, these studies are closely related to the work of one of us, previously published (3, 4). Through a thoroughly independent method we have attained results rather similar to those of Tobian. However, we should like to stress the fact that: i) for the measurement of the urinary corticosteroids, we have made use of a very different method than the one used by Tobian (5); ii) in some cases of pre-eclampsia we have been measuring separately other urinary steroids: pregnanediol (6), alpha-pregnanolons (3, 7, 8) and 17-ketosteroids after the chromatographic separation (7); and iii) we have been able to measure the urinary corticosteroids in 3 eclamptic women *immediately after a series of characteristic crises*. These latest measurements have given extremely high corticosteroid values—about seven times as much per twenty-four hours as is found in normal women in the same period of pregnancy.[1]

From our conclusions (2), we have been so bold as to discuss the pathogenesis of eclampsia. All the symptoms of this disease seem to be explained by an absolute or relative excess of corticosteroids (S hormone of Albright) balanced by a diminution of steroids grouped by Albright under the name of N hormone. From the discussion, it seems that the cause of eclampsia

[1] A first communication of our results was made in the month of February 1949 at meetings of the Laboratoire de Biologie Médicale, University of Louvain, Belgium.

may be found in the lack of hormonal equilibrium, a lack which is peculiar to the period of pregnancy favorable for the eclampsia.

Université de Louvain
Laboratoire de Biologie Médicale,
38, rue des Récollets,
Louvain, Belgium.

RAYMOND DEVIS, M.D.
MARTHE DEVIS-VANDEN EECKHOUDT
June 30, 1949

REFERENCES

1. TOBIAN, L., JR.: Cortical steroid excretion in edema of pregnancy, pre-eclampsia, and essential hypertension, *J. Clin. Endocrinol.* **9:** 319–329, 1949.
2. DEVIS, R., and DEVIS-VANDEN EECKHOUDT, M.: Sur la pathogénie de l'éclampsie: l'excrétion urinaire des "corticostéroïdes" au cours de la pré-éclampsie et de l'éclampsie. Prégnandiolurie et dosage fractionné des 17-CS urinaires, *Ann. d'Endocrinol.* **10:** 1949 (in press).
3. DEVIS, R.: Sur l'origine de la prégnandiolurie dans la deuxième moitié de la grossesse, *Ann. d'Endocrinol.* **10:** 173–179, 1949.
4. DEVIS, R.: Le dosage fractionné des 17-cétostéroïdes urinaires en gynécologie, *Bruxelles-méd.*, **29:** 1568–1584, 1949.
5. HEARD, R. D. H.; SOBEL, H., and VENNING, E. H.: The neutral lipide-soluble reducing substances of urine as an index of adrenal cortical function, *J. Biol. Chem.* **165:** 699–710, 1946.
6. ASTWOOD, E. B., and JONES, G. E. S.: A simple method for the quantitative determination of pregnanediol in human urine, *J. Biol. Chem.* **137:** 397, 1941.
7. DINGEMANSE, E.; HUIS IN'T VELD, L. G., and DE LAAT, B. M.: Clinical method for the chromatographic-colorimetric determination of urinary 17-ketosteroids, *J. Clin. Endocrinol.* **6:** 535–548, 1946.
8. DOBRINER, K.; LIEBERMAN, S., and RHOADS, C. P.: Methods for the isolation and quantitative estimation of neutral steroids present in human urine, *J. Biol. Chem.* **172:** 241–261, 1948.

Postgraduate Assembly in Endocrinology Including Diabetes

Sponsored by

THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

and

THE AMERICAN DIABETES ASSOCIATION

MIAMI BEACH, FLORIDA RONEY PLAZA HOTEL APRIL 3–8, 1950

The faculty will consist of prominent researchers and clinicians in the field of endocrinology and metabolic disorders, from the United States and Canada.

The course will be a practical one of interest and value to the specialist and those in general practice. The program will consist of lectures, clinics and demonstrations. Ample time will be given to questions and answers at the end of each session, and registrants are encouraged to contact members of the faculty for individual discussions.

The Roney Plaza, one of Miami Beach's most delightful hotels, offers special convention rates to members of this assembly. This is an unusual opportunity for you and your family to enjoy a pleasant vacation and for you to participate in a highly instructive program of the latest advances in endocrinology and metabolism.

A fee of $75 will be charged for the entire course and the attendance will be limited to 100. REGISTRATION WILL BE IN THE ORDER OF CHECKS RECEIVED AND WILL CLOSE ON MARCH 3, 1950. Should there be an insufficient number of applicants to fill the course, the registration fee will be refunded immediately in its full amount.

Application for approval of this course has been made to the Veterans Administration. Veterans should make formal application to their local agencies on the appropriate form (1905e or 1950) as furnished by the V.A.

Please forward application on your letterhead, together with check payable to The Association for the Study of Internal Secretions, to Henry H. Turner, M.D., Secretary-Treasurer, 1200 North Walker Street, Oklahoma City 3, Oklahoma, before March 3, 1950. Further information and program will be furnished upon request.

Hotel reservations should be made directly with the Roney Plaza Hotel, Miami Beach, Florida, and the hotel advised that you are attending this Postgraduate Assembly.

The 1950 Meeting of the Association for the Study of Internal Secretions

The Thirty-Second Annual Meeting of The Association for the Study of Internal Secretions will be held at the Sir Francis Drake Hotel, Friday and Saturday, June 23 and 24, 1950, in San Francisco, California.

The Committee on Local Arrangements is comprised of Dr. Hans Lisser, Chairman, and Drs. Leslie L. Bennett, Roberto F. Escamilla, Minnie B. Goldberg, Gilbert S. Gordan, and Laurance W. Kinsell.

Hotel accommodations will be difficult to secure on short notice; therefore, members are urged to make their reservations at once. All requests must be addressed to: Dr. William Howard Rustad, American Medical Association (Hotel Committee), Room 200, Civic Auditorium, San Francisco, California.

The scientific sessions will be held in the Empire Room of the Sir Francis Drake, and registration will be on the same floor. The annual dinner will be held in the Empire Room on Friday, June 23, at 7:30 P.M., preceded by cocktails at 6:30 P.M.

Those wishing to present papers, which will be limited to ten minutes, should send title and four copies of an abstract of not more than 200 words, to Edward A. Doisy, M.D., St. Louis University School of Medicine, 1402 South Grand Avenue, St. Louis, Missouri, not later than *March 1, 1950. It is imperative that the abstracts be informative and complete with results and conclusions in order that they may be of reference value and suitable for printing in the program and journals of the Association.* Names of non-members who are co-authors must be followed by the words "by invitation," and the principal degree of each author.

Nominations for the Ayerst, McKenna and Harrison Fellowship, the Schering Fellowship in Endocrinology, the Squibb Award, and the Ciba Award should be made on special application forms which may be obtained from the Secretary-Treasurer, Henry H. Turner, M.D., 1200 North Walker Street, Oklahoma City 3, Oklahoma, and filed with the Secretary not later than *March 15, 1950.*

The 1950 Awards of the Association for the Study of Internal Secretions

FELLOWSHIPS

The Ayerst, McKenna and Harrison Fellowship

The Ayerst, McKenna and Harrison Fellowship was first awarded in 1947 to Dr. Samuel Dvoskin and in 1948 to Dr. Ernest M. Brown, Jr. Dr. Brown was re-elected for the Fellowship in 1949.

The Schering Fellowship in Endocrinology

The Schering Fellowship in Endocrinology was established in 1949 and the first recipient was Dr. D. Lawrence Wilson.

Association Fellowships are designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. Fellowships may be awarded to an individual who possesses the Ph.D or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $2,500, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals. He must submit a program of proposed study, indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

AWARDS

The E. R. Squibb and Sons Award

The E. R. Squibb & Sons Award of $1,000 was established in 1939, and was given first in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. E. A. Doisy; in 1945

to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori; in 1948 to Dr. Fuller Albright; and in 1949 to Dr. Herbert M. Evans. In 1943 no award was given. A special committee of five members of the Association selects the recipient from among investigators in the United States or Canada, on the basis of outstanding contributions to endocrinology.

The Ciba Award

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than 35 years of age in the field of clinical or preclinical endocrinology was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Heller; and in 1949 to Dr. George Sayers. The Award is for $1,200. If within twenty-four months of the date of the Award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $1,800.

* * * * *

NOMINATIONS

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in endocrinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on *special application forms* which may be obtained from the *Secretary*, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, and returned to him not later than *March 15, 1950.*

The 1950 Meeting of the American Goiter Association

The next annual meeting of the American Goiter Association will be held at the Hotel Shamrock, Houston, Texas, March 9, 10, and 11, 1950.

The program will include among its speakers leaders in all fields of thyroid disease. The Chairman of the Program Committee is Dr. Rulon W. Rawson, Memorial Hospital, 444 East 68th Street, New York 21, N. Y.

All physicians in good standing in their respective medical societies may attend the meeting by registering as attending members. All members or others planning to attend are urged to make their reservations immediately by addressing the Reservation Department of the Hotel Shamrock, Houston, Texas.

Award of the American Goiter Association

VAN METER PRIZE

The American Goiter Association again offers the Van Meter Prize Award of three hundred dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Houston, Texas, March 9, 10 and 11, 1950, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length, and must be presented in English. A typewritten double spaced copy *in duplicate* should be sent to the Corresponding Secretary, Dr. George C. Shivers, 100 East St. Vrain Street, Colorado Springs, Colorado, not later than *January 15, 1950.* The Committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association.

INDEX TO VOLUME 9

AUTHOR INDEX

ABARBANEL, A. R.: Artificial reproduction of the cyclic changes in cervical mucus in human castrates: with clinical correlations, 479

——: Intravenous estrogen in menometrorrhagia in the human, 681†

——: Management of threatened abortion in the human with large doses of diethylstilbestrol, 669†

——; HOYT, R., and LEVINE, M. G.: Pregnanediol excretion in cases of blighted ovum, 676†

ABERNATHY, E., *see* LYONS, W. R., 679†

ADLERSBERG, D. and MAYER, M. E.: Results of prolonged medical treatment of obesity with diet alone, diet and thyroid preparations, and diet and amphetamine, 275*

ALBERT, A. and KEATING, F. R., JR.: Metabolic studies with I^{131} labeled thyroid compounds. Comparison of the distribution and fate of radioactive *d-l*-thyroxine after oral and intravenous administration in the human, 1406*

——; RALL, J. E.; KEATING, F. R., JR.; POWER, M. H., and WILLIAMS, M. M. D. The behavior of labeled thyroglobulin and labeled thyroxine in patients with myxedema, 1392

——, *see* GASTINEAU, C. F., 615*

——, *see* HAMILTON, C. F., 828*

ALBRIEUX, A. S. and MUSSIO FOURNIER, J. C.: (Letter to the Editor) The local action of testosterone propionate on the development of axillary hair in man, 1434*

ALBRIGHT, F., *see* BARTTER, F. C., 663†

——, *see* ELRICK, H., 665†

ALEXANDER, B., *see* VRIES, A. DE., 398

ALEXANDER, S. B. and TUCKER, H. ST. G., JR.: Pseudohypoparathyroidism. Report of a case with late manifestations, 862*

ALTSCHULE, L. H., *see* ALTSCHULE, M. D., 548*

ALTSCHULE, M. D.; ALTSCHULE, L. H., and TILLOTSON, K. J.: Changes in urinary uric acid-creatinine ratio after electrically induced convulsions in man, 548*

——; PARKHURST, B. H., and TILLOTSON, K. J.: Decreases in blood eosinophilic leukocytes after electrically induced convulsions in man, 440*

ANDERSON, E. and HAYMAKER, W.: Studies in carbohydrate metabolism in decerebrate rats, 670†

——; KINSELL, L. W.; DANIELS, T. C., and HENDERSON, E.: The treatment of Addison's disease by the intraoral administration of desoxycorticosterone acetate tablets, 1324*

ARGONZ, J., *see* CASTILLO, E. B. DEL., 1362*

ASTWOOD, E. B., *see* GREER, M. A., 1069*

AYRE, W. B. and AYRE, J. E.: Vaginal smear glycogen: limitations as an index of estrogen activity, 1359*

AYRE, J. E., *see* AYRE, W. B., 1359*

BADER, R. A., *see* STEIN, H. J., 529*

BAKER, J. R., *see* SEARLE, W. N., 112

BAKER, L. A., *see* STONE, H. H., 895*

BALZE, F. A. DE LA: The progesterone withdrawal test or "medical curettage." Diagnosis and classification of amenorrheas, 110

BAMFORD, S., *see* NIEBURGS, H. E., 673†

BARNES, R. H., *see* PALMER, L. J., 395

BARTELS, E. C.: Basal metabolism testing under pentothal anesthesia, 1190*

——: Propylthiouracil; its use in the preoperative treatment of severe and complicated hyperthyroidism, 297

BARTTER, F. C.; FORBES, A. P.; JEFFERIES, W. M.; CARROLL, E. L., and ALBRIGHT, F.: The mechanism of action of testosterone in the therapy of Cushing's syndrome, 663†

——, *see* ELRICK, H., 665†

BAS, J. A., *see* SCHWEITZER, F. L., 297

BASS, D. E., *see* STEIN, H. J., 529*

BATES, R. W., *see* COHEN, H., 667†

BEIRNE, D. P., *see* SCHWARTZMAN, J., 396

BELLER, C. and TURNER, H. H.: Effects of

* Original article.

† Abstract of paper presented at the Thirty-first Annual Meeting of The Association for the Study of Internal Secretions.

Other items are abstracts of articles which appeared in current medical journals and miscellaneous entries.

small doses of testosterone propionate on spermatogenesis, 666†
BENDER, S.: The value of the Guterman test in threatened abortion, 110
BENNETT, L. L.; SLESSOR, A., and THORN, G. W.: Effect of compound E on blood ketone bodies, 675†
——, *see* FORSHAM, P. H., 660†
BENNETT, W. A., *see* RALL, J. E., 1379*
——, *see* SPRAGUE, R. G., 672†
BERGMANN, A. J. and MILLER, L. C.: The androgenic activity of new esters of testosterone, 679†
BERGNER, G. E., *see* SWANK, R. L., 401
BERTHRONG, M.; GOODWIN, W. E., and SCOTT, W. W.: Estrogen production by the testis, 579*
BICKERS, W.: Progesterone: a comparison of intramuscular, oral and sublingual routes of administration, 736*
BIRNIE, J. H., *see* BOSS, W. R., 658†
BISKIND, G. R. and BISKIND, M. S.: The effect of castration, of unilateral castration, and of pregnancy in unilaterally castrate rats on the ovary transplanted into the spleen, 667†
BISKIND, M. S., *see* BISKIND, G. R., 667†
BLACK, B. M.: Surgical treatment of carcinoma of the thyroid gland, 1422*
——, *see* WHITESELL, F. B., JR., 1202*
BLACK, H. M., *see* GOLDSMITH, E. D., 674†
BLACK, R., *see* ZONDEK, B., 402
BLOCK. P., *see* SALTER, W. T., 1080*
BLOOM, W.: Pituitary implications in hypertrophic pulmonary osteoarthropathy, 297
BOAS, N. F. and JAILER, J. W.: On the inability of adrenocorticotropic hormone or epinephrine to deplete the ascorbic acid of the chick adrenal, 655†
BOEKELMAN, A. J.: The thyroid as a regulator of potassium metabolism, 106
BOSS, W. R.; BIRNIE, J. H., and GAUNT, R.: Renal function in normal and adrenalectomized rats following saline or adrenal steroid administration, 658†
BOWERS, J. Z.: Hyperthyroidism occurring at an early age in dissimilar twins, 298
BOYLE, D., *see* PASCHKIS, K. E., 658†
BRADBURY, J. T., *see* LEATHEM, J. H., 385*
——, *see* BROWN, W. E., 725*
BRADY, R. O., *see* RICHARDS, C. E., 1107*
BROCKHURST, R. J., *see* RICHARDS, C. E., 446*
BROH-KAHN, R. H., *see* MIRSKY, I. A., 395
BROOKS, J., *see* FANCHER, J. K., 682†
BROWN, E. J., JR.: Recipient of the 1941 Ayerst, McKenna and Harrison fellowship of the Association for the Study of Internal Secretions, 685
BROWN, W. E. and BRADBURY, J. T.: The use of the human vaginal smear in the assay of estrogens, 725*
BRUNS, H. J., *see* HURXTHAL, L. M., 1245*
BRZEZINSKI, A., *see* ZONDEK, B., 402
BUKA, R., *see* FREEDBERG, A. S., 841*
BURNETT, C. H.; BURROWS, B. A., and COMMONS, R. R.: A mechanism of potassium deficiency in alkalosis, 676†
BURNS, T. W., *see* SAYERS, G., 593*
BURROWS, B. A., *see* BURNETT, C. H., 676†

CAHILL, G. F.: Pheochromocytomas, 108
CALKINS, E.; DANA, G. W.; SEED, J. C., and HOWARD, J. E.: Piperido-methylbenzodioxane (933-F): Some pharmacological and experimental observations, 651†
CAMES, O., *see* STAFFIERI, J. J., 255*
CAÑADELL, J. M., *see* VILANOVA, X., 883*
CANTAROW, A., *see* D'ANGELO, S. A., 653†
——, *see* PASCHKIS, K. E., 658†
CAREN, R.: The goitrogens in thyrotoxicosis complicating pregnancy. A case report, 903*
CAREY, R. A., *see* HOWARD, J. E., 691*
CARROLL, E. L., *see* BARTTER, F. C., 663†
——, *see* FORBES, A. P., 680†
CASTILLO, E. B. DEL.; ARGONZ, J., and GALLI MAININI, C.: Smears from the female urethra and their relationship to smears of the urinary sediment, 1362*
CATTELL, R. B.: Surgical treatment of hyperthyroidism, 999*
CHAMBERS, W. L.: Adrenal cortical carcinoma in a male with excess gonadotropin in the urine, 451*
CHAPMAN, E. M.: Treatment of Graves' disease with radioactive iodine, 298
CHARLES, C. M., *see* EDWARDS, J. C., 655†
CHENG, CHI-PING: Regulation of pituitary adrenocorticotropic activity by adrenal cortical hormones, 656†
CID, J. M., *see* STAFFIERI, J. J., 255*
CLARK, S., *see* GREENBLATT, R. B., 668†
COHEN, H. and BATES, R. W.: The occurrence of conjugated sulfates of estrogens in human pregnancy urine, 667†
COHN, C., *see* WOLFSON, W. Q., 497*, 666†, 749*
COLE, W. H.; MAJARAKIS, J. D., and SLAUGHTER, D. P.: Incidence of carcinoma of the thyroid in nodular goiter, 1007*
COLEMAN, T. H., *see* RICHARDS, C. E., 446*
COLVIN, F. M., *see* TIPTON, S. R., 684†
COMMONS, R. R., *see* BURNETT, C. H., 676†
CONN, J. W. and VOGEL, W. C.: Effects of prolonged adrenal cortical stimulation upon free and esterified serum cholesterol in normal men, 656†

CONNOR, A. C.; CURTIS, G. M., and SWENSON, R. E.: A simplified method for the determination of the protein-bound blood iodine and its clinical application, 1185*
COOPER, I. S. and HOEN, T. I.: Gynecomastia in paraplegic males. Report of seven cases, 457*
COPE, O.; DOBYNS, B. M.; HAMLIN, E., JR., and HOPKIRK, J.: What thyroid nodules are to be feared?, 1012*
COPPEDGE, R. L. and SEGALOFF, A.: A method for the assay of prolactin in human urine, 653†
CORTELL, R.: Second honorable mention for the 1949 Van Meter prize award of the American Goiter Association, 688
——: The antithyroxine activity of thyroxine analogs, 955*
COVIAN, M. R.: Role of emotional stress in the survival of adrenalectomized rats given replacement therapy, 678†
CRAMPTON, J. H.; SCUDDER, S. T., and DAVIS, C. D.: Carbohydrate metabolism in the combination of diabetes mellitus and Addison's disease, as illustrated by a case, 245*
——, *see* PALMER, L. J., 395
CRILE, G., JR., *see* HAZARD, J. B., 1216*
CRUMRINE, J. L., *see* PRESTON, F. W., 1314*
CRUSIUS, M. E., *see* SCHWARTZMAN, J., 396
CURTIS, G. M., *see* CONNOR, A. C., 1185*

DANA, G. W., *see* CALKINS, E., 651†
D'ANGELO. S. A.; GORDON, A. S.; PASCHKIS, K. E., and CANTAROW, A.: Thyrotropic and thyroid hormone assay of normal and pathologic human sera in the stasis tadpole, 653†
DANIELS, T. C., *see* ANDERSON, E., 1324*
DANOWSKI, T. S.; HEDENBURG, S., and GREENMAN, J. H.: The constancy of the serum precipitable or protein-bound iodine in healthy adults, 768*
DANZIGER, L. and KINDWALL, J. A.: Thyroid therapy in some mental disorders, 298
DAUGHADAY, W. H. and MACBRYDE, C. M.: Changes in urinary steroids produced by sodium deprivation and by desoxycorticosterone acetate administration, 661†
DAVENPORT, H. W., *see* SAYERS, G., 593*
DAVIS, C. D., *see* CRAMPTON, J. H., 245*
DAVIS, M. E. and HULIT, B. E.: Changes in circulating eosinophils in women during the menstrual cycle and reproduction, 714*
DAVISON, R. A.; KOETS, P., and KUZELL, W. C.: Effect of roentgenotherapy on urinary 17-ketosteroid excretion in ankylosing spondylarthritis, 79*
DAVISON, T. C. and LETTON, A. H.: Hashimoto's disease, 980*
DEAL, R. V., *see* KINSELL, L. W., 671†
DE LA BALZE, F. A., *see* BALZE, F. DE LA
DEL CASTILLO, E. B., *see* CASTILLO, E. B. DEL
DELFS, E., *see* JONES, G. E. S., 743*
DEMPSEY, E. F., *see* FOURMAN, P., 660†
DEMPSEY, W. S., *see* DINSMORE, R. S., 1043*
——, *see* HAZARD, J. B., 1216*
DE ROBERTIS, E., *see* ROBERTIS, E. DE
DEVIS-VANDEN EECKHOUDT, M., *see* DEVIS, R., 1436*
DEVIS, R. and DEVIS-VANDEN EECKHOUDT, M.: (Letter to the Editor) The urinary corticosteroid excretion in pre-eclampsia and eclampsia, 1436*
DE VRIES, A., *see* VRIES A. DE
DINSMORE, R. S.; DEMPSEY, W. S., and HAZARD, J. B.: Lymphosarcoma of the thyroid, 1043*
DOBYNS, B. M.; SKANSE, B., and MALOOF, F.: A method for the preoperative estimation of function in thyroid tumors; its significance in diagnosis and treatment, 1171*
——, *see* COPE, O., 1012*
DONOVAN, T. J., *see* ZIMMERMANN, B., 398
DREKTER, I. J., *see* WEISSBERG, J., 673†, 1259*
DUFFY, B. J., *see* TRUNNELL, J. B., 1138*
DUMM, M. E.; ROTH, P.; OVANDO, P., and RALLI, E. P.: The white blood cell response of rats to adrenalectomy, stress and pantothenic acid, 678†
——, *see* RALLI, E. P., 652†

EATON, J. C., *see* MUNRO, H. N., 48*
EDWARDS, J. C.; CHARLES, C. M., and MACBRYDE, C. M.: The evaluation of the use of the anterior pituitary extract in the treatment of pituitary dwarfism, 655†
ELIOT, J. W., *see* STEIN, H. J., 529*
ELRICK, H.; BARTTER, F. C.; SUTPHIN, A., and ALBRIGHT, F.: Pseudo-hypoparathyroidism: a report of two new cases with special reference to the epiphyseal changes, 665†
ENGEL, F. L.: Stimulation of nitrogen metabolism by adrenal cortical extract during insulin hypoglycemia, 657†
——, *see* TEABEAUT, R., 663†
ENGELMAN, M., *see* TWOMBLY, G. H., 112
ESCARDÓ, F., *see* REFORZO-MEMBRIVES, J., 1333*
ESCHER, G. C., *see* TALBOT, T. R., JR., 666†
ETTLINGER, M. C., *see* GREER, M. A., 1069*
EVA, M. L., *see* LLOYD, C. W., 268*
EVANS, H. M.: Recipient of the 1949 Squibb

award of the Association for the Study of Internal Secretions, 686

FABER, M., *see* GOLDENBERG, M., 652†
FABRYHART, M. and PACELLA, B. L.: Association of spontaneous hypocalcemia and electrocerebral dysfunction, 398
FANCHER, J. K. and BROOKS, J.: The incidence of cancer in endocrine case histories, 682†
FARRIS, E. J.: The prediction of the day of human ovulation by the rat test as confirmed by fifty conceptions, 110
FINKLER, R. S.: The effect of vitamin E in the menopause, 89*
FITZGERALD, P. K. and FOOTE, F. W., JR.: The function of various types of thyroid carcinoma as revealed by the radioautographic demonstration of radioactive iodine (I^{131}), 1153*
FLANAGAN, E. K., *see* MARGEN, S., 662†
FLINK, E. B., *see* FORSHAM, P. H., 660†
FLUHARTY, R. G., *see* MCARTHUR, J. W., 299
FOOTE, FRANK W., JR., *see* FITZGERALD, P. J., 1153*
——, *see* FRAZELL, EDGAR L., 1023*
FORBES, A. P.; CARROLL, E. L., and WHEELER, M. L.: A comparison of the 17-ketosteroid excretion of cases of Cushing's syndrome due to adrenal tumor with those due to hyperplasia (hyperfunction), 680†
——, *see* BARTTER, F. C., 663†
FORD, N. W., *see* LEECH, R. S., 394
FOREMAN, N., *see* SOLEY, M. H., 29*
FORSHAM, P. H.; BENNETT, L. L.; ROCHE, M.; REISS, R. S.; SLESSOR, A.; FLINK, E. B., and THORN, G. W.: Clinical and metabolic changes in Addison's disease following the administration of compound E acetate (11-dehydro, 17-hydroxy-corticosterone acetate), 660†
——, *see* REISS, R. S., 659†
——, *see* THORN, G. W., 109
FOSTER, W. C., *see* MCCLENDON, J. F., 680†
FOURMAN, P.; KEPLER, E. J.; REIFENSTEIN, E. C., JR., and DEMPSEY, E. F.: Effect of a single dose of desoxycorticosterone acetate on electrolyte metabolism, 660†
FOURNIER, J. C. MUSSIO, *see* MUSSIO FOURNIER, J. C.
FRANKEL, J. J., *see* STONE, H. H., 895*
FRANKLIN, W. and LOWELL, F. C.: On the preparation of human insulin for experimental use, 481*
FRAZELL, E. L. and FOOTE, F. W., JR.: The natural history of thyroid cancer. A review of 301 cases, 1023*
FREEDBERG, A. S.; BUKA, R., and MCMANUS, M. J.: Comparative value and accuracy of measurements of urinary I^{131} by beta and by gamma ray counting, 841*
FRIED, P. H.: The two hour pregnancy test, based on rat ovary hyperemia, 479
——, *see* RAKOFF, A. E., 668†
FRIEDMAN, C. L., *see* FRIEDMAN, S. M., 109
FRIEDMAN, N. B.: Cellular involution in the thyroid gland. Significance of Hürthle cells in myxedema, exhaustion atrophy, Hashimoto's disease and the reactions to irradiation, thiouracil therapy and subtotal resection, 874*
FRIEDMAN, S. M.; FRIEDMAN, C. L., and POLLEY, J. R.: Potentiation of the hypertensive effects of desoxycorticosterone acetate by various sodium salts, 109
FUNNELL, J. W., *see* HELLBAUM, A. A., 668†
FUTCHER, P. H., *see* GOLDMAN, M. L., 622*
——, *see* KRISS, J. P., 13*

GALLI MAININI, C.: Pregnancy test using the male batrachia, 399
——, *see* CASTILLO, E. B. DEL, 1362*
GASTINEAU, C. F.; ALBERT, A., and RANDALL, L. M.: The renal clearance of chorionic gonadotropic hormone in pregnancy, in neoplasm of the testis and in hydatidiform mole, 615*
GAUNT, R., *see* BOSS, W. R., 658†
GERMAN, W. J., *see* PETERS, J. P., 1292*
GERSTNER, R. and GORDON, A. S.: Effects of hemopoietic agents on blood formation in hypophysectomized rats, 676†
GLEN, A., *see* MUNRO, H. N., 48*
GOLDENBERG, M. and FABER, M.: Norepinephrine in adrenal medulla, 652†
GOLDMAN, M. L.; SCHROEDER, H. A., and FUTCHER, P. H.: Coarctation of the aorta associated with abnormal digits, ovarian insufficiency and shortness of stature, 622*
GOLDSMITH, E. D.; BLACK, H. M., and NIGRELLI, R. F.: The effect of pteroylglutamic acid antagonists on the response of the reproductive accessories of C57 male mice to testosterone, 674†
GOLDZIEHER, J. W.: A new colorimetric method for the determination of pregnandiol, 399
—— and STONE, G. C. H.: A rapid colorimetric method for the determination of sodium in biological fluids, 95*
—— and STONE, G. C. H.: The relative independence of sodium and chloride excretion, 368*
GOODWIN, L. D., *see* WERNER, S. C., 664†
GOODWIN, W. E., *see* BERTHRONG, M., 579*
GORDON, A. S., *see* D'ANGELO, S. A., 653†

——, *see* GERSTNER, R., 676†
GREEN, D. M.: Mechanisms of desoxycorticosterone action, 478
GREENBLATT, R. B.; CLARK, S., and WEST, R. M.: Hormonal factors producing the gametokinetic response in the male frog (Rana pipiens), 668†
——, *see* NIEBURGS, H. E., 673†
GREENMAN, J. H., *see* DANOWSKI, T. S., 768*
GREENWALD, I.: The problem of endemic goiter in Yunnan province, 684†
GREER, M. A.; ETTLINGER, M. G., and ASTWOOD, E. B.: Dietary factors in the pathogenesis of simple goiter, 1069*
GROPPER, M., *see* LYONS, W. R., 679†
GROSS, J., *see* LEBLOND, C. P., 149*
GUTERMAN, H. S. and SCHROEDER, M. S.: A simplified technique for the quantitative colorimetric estimation of pregnandiol in urine, 479
——, *see* WOLFSON, W. Q., 497*, 749*

HAIN, A. M.: An unusual case of precocious puberty associated with ovarian dysgerminoma, 1349*
HAINES, M., *see* SEARLE, W. N., 112
HAINES, S. F., *see* HAMILTON, C. F., 828*
——, *see* KELSEY, M. P., 171*
——, *see* PEMBERTON, JOHN DEJ., 1232*
HALBRECHT, J.: Further observations on the basal temperature in sterile women, 110
HALL, G. J.: (Letter to the Editor) The buccal administration of estradiol, 382*
HAMILTON, C. F.; ALBERT, A.; POWER, M. H.; HAINES, S. F., and KEATING, F. R., JR.: The behavior of labeled iodocasein in human myxedema, 828*
HAMILTON, J. B.: Quantitative measurements of the growth of axillary hair as an index of the endocrine status, 665†
HAMLIN, E., JR., *see* COPE, O., 1012*
HARE, H. F., *see* HURXTHAL, L. M., 126*
HARINGTON, C. R., *see* LERMAN, J., 1099*
HAVEL, L., *see* HORLICK, L., 106
HAYLES, A. B., *see* SPRAGUE, R. G., 672†
HAYMAKER, W., *see* ANDERSON, E., 670†
HAZARD, J. B.; CRILE, G., JR., and DEMPSEY, W. S.: Nonencapsulated sclerosing tumors of the thyroid, 1216*
——, *see* DINSMORE, R. S., 1043*
HECKEL, G. P.: The problem of allergy to steroid hormones, 681†
HEDENBURG, S., *see* DANOWSKI, T. S., 768*
HEFTMANN, E., *see* WILKERSON, H. L. C., 397
HEINEMANN, M.; JOHNSON, C. E., and MAN, E. B.: Serum precipitable iodine concentrations during pregnancy, 299
HELLBAUM, A. A.; FUNNELL, J. W., and KEATY, E. C.: Action of estrogens on release of luteinizing hormone in menopausal women, 668†
HELLER, C. G., *see* JUNGCK, E. C., 355*
HELMREICH, M. L., *see* SAMUELS, L. T., 674†
HENDERSON, E., *see* ANDERSON, E., 1324*
HERRMAN, J. B.; KIRSTEN, E., and KRAKAUER, J. S.: Hypercalcemic syndrome associated with androgenic and estrogenic therapy, 1*
HERTZ, J.: Studies on thyrotoxicosis, 299
HIBBS, R. E., *see* MCCULLAGH, E. P., 107
HILES, C.: Gastric secretory response in hypoglycemia as produced during insulin shock therapy, 394
HILL, R., *see* TRUNNELL, J. B., 1138*
HILLS, A. G., *see* THORN, G. W., 109
——, *see* ROCHE, M., 662†
HOEN, T. I., *see* COOPER, I. S., 457*
HOFFMAN, M. M., *see* MCINTOSH, H. W., 661†
——, *see* WALSH, G. C., 670†
HOLLANDER, G. H. and MANDELBAUM, H.: The treatment of angina pectoris with propylthiouracil, 106
HOPKIRK, J., *see* COPE, O., 1012*
HORLICK, L. and HAVEL, L.: The effect of feeding propylthiouracil and cholesterol on the blood cholesterol and arterial intima in the rat, 106
HORRAX, G., *see* HURXTHAL, L. M., 126*
HOSKINS, R. G.: (Editorial) More light on the biochemistry of diabetes, 1238*
——: (Editorial) The thyroid-pituitary apparatus as a servo (feed-back) mechanism, 1429*
HOWARD, J. E. and CAREY, R. A.: The use of potassium in therapy, 691*
——, *see* CALKINS, E., 651†
HOYT, R., *see* ABARBANEL, A. R., 676†
HRUBY, F. J., *see* MCCULLAGH, E. P., 113*
HUDDLESTUN, B., *see* WOLFSON, W. Q., 749*
HUGHES, E. C., *see* LLOYD, C. W., 268*, 636*, 654†
HULIT, B. E., *see* DAVIS, M. E., 714*
HUNT, H. D., *see* WOLFSON, W. Q., 497*, 749*
HURXTHAL, L. M.; HARE, H. F.; HORRAX, G., and POPPEN, J. L.: The treatment of acromegaly, 126*
——; BRUNS, H. J., and MUSULIN, N.: Development of spermatogenesis in hypogonadism, 1245*

JACKSON, A. S.: Henry S. Plummer, M. D., 967*
JAFFE, H., *see* WILLIAMS, R. H., 801*
JAGER, B. V., *see* SAYERS, G., 593*
JAILER, J. W.: The metabolism of the estrogens: a review, 557*
——: The effect of dietary protein on the

ability of the liver to inactivate estradiol in the rat, 675†
——, *see* BOAS, N. F., 655†
——, *see* KNOWLTON, A. I., 514*
JEFFERIES, W. M.: Recipient of the 1949 Van Meter prize award of the American Goiter Association, 687
——: Studies of the relationship of the thyrotropic, exophthalmic and fat-mobilizing principles of pituitary extract. I. The effect of various dosages of pituitary extract upon the production of exophthalmos and the mobilization of fat in intact and thyroidectomized guinea pigs, 913*
——: II. The effect of iodination of pituitary extract upon these three principles, 927*
——: III. The effect of adrenocorticotropic hormone (ACTH) and desoxycorticosterone acetate (DOCA) upon exophthalmos and fat mobilization in guinea pigs, 937*
——, *see* BARTTER, F. C., 663†
JOHNSON, B., *see* LESLIE, S. H., 682†
JOHNSON, C. E., *see* HEINEMANN, M., 299
JONES, G. E. S.; DELFS, E., and STRAN, H. M.: The effect of alpha-tocopherol administration on pregnanediol excretion, 743*
JOSEPH, H., *see* TOBIAN, L., JR., 677†
JUNGCK, E. C.; MADDOCK, W. O.; HELLER, C. G., and NELSON, W. O.: Antihormone formation complicating pituitary gonadotropin therapy in infertile men. II. Effect on number of sperm, morphology of the testis and urinary gonadotropins, 355*

KADOTA, K., *see* WOLFSON, W. Q., 497*, 666†, 749*
KANTER, A. E. and KLAWANS, A. H.: Shock from posterior pituitary extract, 106
KARANDIKAR, G., *see* SALTER, W. T., 1080*
KAY, G. A., *see* WILLIAMS, R. H., 107
KAZMIN, V. E., *see* VENNING, E. H., 659†
KEATING, F. R., JR., *see* ALBERT, A., 1406*
——, *see* HAMILTON, C. F., 828*
——, *see* KELSEY, M. P., 171*
——, *see* PEMBERTON, J. DEJ., 1232*
——, *see* RALL, J. E., 1379*
KEATING, R. P., *see* SCHULMAN, J., JR., 664†
KEATY, E. C., *see* HELLBAUM, A. A., 668†
KELSEY, M. P.; HAINES, S. F., and KEATING, F. R., JR.: Radioiodine in the study and treatment of thyroid disease: a review, 171*
KENIGSBERG, S.; PEARSON, S., and MCGAVACK, T. H.: The excretion of 17-ketosteroids. I. Normal values in relation to age and sex, 426*
KEPLER, E. J., *see* FOURMAN, P., 660†
KEUTMANN, E. H., *see* WATERHOUSE, C., 109
KINDWALL, J. A., *see* DANZIGER, L., 298
KINSELL, L. W.; MARGEN, S.; MICHAELS, G. D.; SIGNOROTTI, B. T., and MCCALLIE, D. P.; with the technical assistance of THOMPSON, V. T.; DEAL, R. V., and LODUCA, P.: Studies in fat metabolism. I. Steroid hormonal effects upon blood ketones and other intermediate products of fat and protein catabolism, 671†
——, *see* ANDERSON, E., 1324*
——, *see* MARGEN, S., 662†
KIRSCH, H., *see* TYLER, E. T., 480
KIRSNER, J. B., *see* LEVIN, E., 399
KIRSTEN, E., *see* HERRMANN, J. B., 1*
KLAWANS, A. H., *see* KANTER, A. E., 106
KNIGHT, W. R.: Theca-cell tumors of the ovary with a report of 15 cases and a review of the literature, 111
KNOWLTON, A. I. and KRITZLER, R. A.: The development of diabetes mellitus in Addison's disease. Case report with autopsy, 36*
KNOWLTON, A. I.; MUDGE, G. H., and JAILER, J. W.: Pregnancy in Addison's disease. Report of four patients, 514*
KOETS, P.: The excretion of 17-ketosteroids in idiopathic hirsutism, 795*
——, *see* DAVISON, R. A., 79*
KOREF, O., *see* VARGAS, L., 818*
KRAKAUER, K. S., *see* HERRMANN, J. B., 1*
KREVSKY, D., *see* WOLFSON, W. Q., 666†
KRISS, J. P. and FUTCHER, P. H.: Renal excretion and reabsorption of salt in Cushing's syndrome after intravenous administration of hypertonic sodium chloride, 13*
KRITZLER, R. A., *see* KNOWLTON, A. I., 36*
KULLANDER, S.: Investigations into the determination of pregnanediol according to the Guterman method, 111
KUZELL, W. C., *see* DAVISON, R. A., 79*

LADUE, J. S.; MURISON, P. J., and PACK, G. T.: The use of tetraethylammonium bromide as a diagnostic test for pheochromocytoma, 478
LAKEN, B., *see* RALLI, E. P., 652†
LEATHEM, J. H. and BRADBURY, J. T.: (Letter to the Editor) Antihormone formation during chorionic gonadotropin therapy, 385*
—— and RAKOFF, A. E.: Further studies of antigonadotropin formation in man, 654†
LEBLOND, C. P. and GROSS, J.: The mechanism of the secretion of thyroid hormone, 149*
LECOMPTE, P. M.: Width of adrenal cortex in lymphatic leukemia, lymphosarcoma and hyperthyroidism, 158*

LEECH, R. S. and FORD, N. W.: A simple bedside method for the estimation of blood sugar, 394
LERMAN, J. and HARINGTON, C. R.: Physiologic activity of tetrabromthyronine and tetrachlorthyronine, 1099*
LESLIE, S. H.; JOHNSON, B., and RALLI, E. P.: Renal clearances in patients with cirrhosis of the liver, with and without ascites, 682†
——, *see* RALLI, E. P., 652†
LETTON, A. H., *see* DAVISON, T. C., 980*
LEVEDAHL, B. H., *see* SAMUELS, L. T., 674†
LEVIN, E.; KIRSNER, J. B., and PALMER, W. L.: Preliminary observations on histamine and insulin stimulated gastric secretion during the injection of an enterogastrone concentrate in man, 399
LEVIN, L.: The possible involvement of the adrenal cortex and thyroid in mobilization of fat to the liver, 657†
LEVINE, M. G., *see* ABARBANEL, A. R., 676†
LEVINE, R., *see* WOLFSON, W. Q., 497*, 666†, 749*
LLOYD, C. W.; HUGHES, E. C.; EVA, M. L., and LOBOTSKY, K.: The urinary excretion of chorionic gonadotropin by human females following parenteral administration of aqueous or beeswax solutions, 268*
——; MORLEY, M.; MORROW, K.; LOBOTSKY, J., and HUGHES, E. C.: Estimation of urinary gonadotropin of the nonpregnant human by the mouse uterine weight and ovarian hyperemia responses, 636*, 654†
LOBOTSKY, J., *see* LLOYD, C. W., 268*, 636*, 654†
LODUCA, P., *see* KINSELL, L. W., 671†
LOESER, A. A.: The action of intravenously injected sex hormones and other substances on the blood flow in the human endometrium, 111
LONGWELL, B. B., *see* MATSON, C. F., 646*
LOWELL, F. C., *see* FRANKLIN, W., 481*
LUGOVOY, J. K., *see* PINCUS, J. B., 400
LUSSICH SIRI, J. J., *see* MUSSIO FOURNIER, J. C., 555*
LYONS, W. R.; ABERNATHY, E., and GROPPER, M.: Effect of androgen and growth hormone on the rat's os penis, 679†

MACBRYDE, C. M., *see* EDWARDS, J. C., 655†
——, *see* DAUGHADAY, W. H., 661†
MACK, H. C.; PARKS, A. E., and MCDONALD, M.: The pregnandiol precipitation test. Further observations on clinical applications and technic, 234*
MADDOCK, W. O.: Antihormone formation complicating pituitary gonadotropin therapy in infertile men, 213*
——, *see* JUNGCK, E. C., 355*
MAJARAKIS, J. D., *see* COLE, W. H., 1007*
MAININI, C. GALLI, *see* GALLI MAININI, C.
MALOOF, F., *see* DOBYNS, B. M., 1171*
MAN, E. B., *see* HEINEMANN, M., 299
——, *see* PETERS, J. P., 107, 1292*
——, *see* ROBBINS, C. L., 377*
MANDELBAUM, H., *see* HOLLANDER, G. H., 106
MANDERNACH, D. M., *see* THOMPSON, W. O., 300
MANNING, J. C., JR., *see* WINSAUER, H. J., 774*
MARGEN, S.; KINSELL, L. W.; FLANAGAN, E. K.; SUITER, L. E., and RAPAPORT, E., with the technical assistance of THOMPSON, V. T.: Is the protein metabolic abnormality of Cushing's syndrome catabolic or anti-anabolic? 662†
——, *see* KINSELL, L. W., 671†
MARINELLI, L. D., *see* TRUNNELL, J. B., 1138*
MASON, E. H., *see* WALSH, G. C., 670†
MASON, H. L. and SPRAGUE, R. G.: Isolation of 17-hydroxycorticosterone from the urine in a case of Cushing's syndrome associated with severe diabetes mellitus, 478
——, *see* MCARTHUR, J. W., 672†
——, *see* SPRAGUE, R. G., 672†
MATSON, C. F. and LONGWELL, B. B.: The excretion of neutral lipid-soluble reducing substances by infants, 646*
MAYER, M. E., *see* ADLERSBERG, D., 275*
MCALPINE, H. T., *see* WALSH, G. C., 670†
MCARTHUR, J. W.; RAWSON, R. W.; FLUHARTY, R. G., and MEANS, J. H.: The urinary excretion of radioactive iodine as an aid in the diagnosis of hyperthyroidism, 299
——; SPRAGUE, R. G., and MASON, H. L.: The urinary excretion of corticosteroids in diabetic acidosis, 672†
MCCALLIE, D. P., *see* KINSELL, L. W., 671†
MCCLENDON, J. F.; FOSTER, W. C., and REED, E.: The "thiocyanate space" and "iodide space" in the thyroid gland, 680†
MCCLINTOCK, L., *see* TWOMBLY, G. H., 112
MCCULLAGH, E. P.; HIBBS, R. E., and SCHNEIDER, R. W.: Propylthiouracil in the treatment of hyperthyroidism, 107
—— and HRUBY, F. J.: Testis-pituitary interrelationship. The relative inability of testosterone to reduce urinary gonadotropin in eunuchoid men, 113*
MCDONALD, M., *see* MACK, H. C., 234*
MCEACHERN, D., *see* WAUGH, D., 486*

McGAVACK, T. H., *see* KENIGSBERG, S., 426*
——, *see* VOGEL, M., 480
——, *see* WEISSBERG, J., 673†, 1259*
McHENRY, E. W.; SEMMONS, E. M.; PEARSE, R., and MEYER, E. G.: Observations on the ketosteroid content of urine from patients with prostatic carcinoma and adenoma, 399
McINTOSH, H. W.; SINGER, B., and HOFFMAN, M. M.: The evaluation of adrenocortical function by ascertaining the response to a single injection of adrenocorticotropin, 661†
McMANUS, M. J., *see* FREEDBERG, A. S., 841*
MEANS, J. H.: Confessions of an elderly thyroidologist, 974*
——: Present day trends in thyroid research, 300
——: (Letter to the Editor) Thyrotoxicosis factitia, 1432*
——, *see* McARTHUR, J. W., 299
MEISTER, L., *see* STARR, P., 330*
MELICOW, M. M.: The role of the adrenal cortex in some somato-sexual aberrations in infants and children, 674†
MELLO, M. I.: Care and maintenance of toads and frogs in captivity, for the performance of Galli Mainini's pregnancy test, 1372*
MELLOW, J., *see* VOGEL, M., 480
MERCHANTE, F. R.: Pregnancy test with the reaction of Galli Mainini, 400
MEYER, E. G., *see* McHENRY, E. W., 399
MICHAELS, G. D., *see* KINSELL, L. W., 671†
MILLARD, E. B. and ROOT, H. F.: Degenerative vascular lesions and diabetes mellitus, 394
MILLER, E. R., *see* SOLEY, M. H., 29*
MILLER, L. C., *see* BERGMANN, A. J., 679†
MIRSKY, I. A.; PODORE, C.J.; WACHMAN, J., and BROH-KAHN, R. H.: The urinary excretion of insulin by normal and diabetic subjects, 395
MOEHLIG, R. C.: (Letter to the Editor) Insulin therapy for relief of pain in osteitis deformans, 385*
MORISON, C. R.: An investigation of the causes of sterility and lowered fertility in West African Negroes, 111
MORLEY, M., *see* LLOYD, C. W., 636*, 654†
MORROW, K., *see* LLOYD, C. W., 636*, 654†
MOSENTHAL, H. O.: Management of diabetes mellitus; an analysis of present day methods of treatment, 395
MUDGE, G. H., *see* KNOWLTON, A. I., 514*
MUNRO, H. N.; EATON, J. C., and GLEN, A.: Survey of a Scottish diabetic clinic. A study of the etiology of diabetes mellitus, 48*
MURISON, P. J., *see* LaDUE, J. S., 478
MUSSIO FOURNIER, J. C.; POLLACK, E., and LUSSICH SIRI, J. J.: Loss of axillary and pubic hair in a patient with Addison's disease and regular menstruation, 555*
—— and POU DE SANTIAGO, A.: Utero-tubal persufflation curve in myxedema. Effect of thyroid therapy, 285*
——, *see* ALBRIEUX, A. S., 1434*
MUSULIN, N., *see* HURXTHAL, L. M., 1245*

NATELSON, S., *see* PINCUS, J. B., 400
NELSON, W. O., *see* JUNGCK, E. C., 355*
NIEBURGS, H. E.; GREENBLATT, R. B., and BAMFORD, S.: Correlation of vaginal smears and endometrial biopsies in normal cycles and in gynecic disorders, 673†
NIGRELLI, R. F., *see* GOLDSMITH, E. D., 674†

OSHRY, E., *see* SEIDLIN, S. M., 1122*
OVANDO, P., *see* DUMM, M. E., 678†

PACELLA, B. L., *see* FABRYHART, M., 398
PACK, G. T., *see* LaDUE, J. S., 478
PALMER, L. J.; CRAMPTON, J. H., and BARNES, R. H.: Pregnancy in the diabetic, 395
PALMER, W. L., *see* LEVIN, E., 399
PARKHURST, B. H., *see* ALTSCHULE, M. D., 440*
PARKS, A. E., *see* MACK, H. C., 234*
PARSON, W., *see* SEGALOFF, A., 1273*
PASCHKIS, K. E.; CANTAROW, A., and BOYLE, D.: Adrenal cortical hormone in blood, 658†
——, *see* D'ANGELO, S. A., 653†
PAYNE, S., *see* TYLER, E. T., 480
PEACOCK, W., *see* TRUNNELL, J. B., 1138*
PEARSE, R., *see* McHENRY, E. W., 399
PEARSON, S., *see* KENIGSBERG, S., 426*
PEMBERTON, J. deJ.; HAINES, S. F., and KEATING, F. R., JR.: The current treatment of hyperthyroidism, A., 1232*
PERLMAN, R. M.: Spermatogenesis following the administration of androgen and gonadotropin in a case of eunuchoidism. Coincidental neoplasm during therapy, 163*
PERLMUTTER, M. and RIGGS, D. S.: Thyroid collection of radioactive iodine and serum protein-bound iodine concentration in senescence, in hypothyroidism and in hypopituitarism, 430*
PETERS, J. P.; GERMAN, W. J., and MAN, E. B.: Serum precipitable iodine in patients with tumors of or near the pituitary, 1292*
—— and MAN, E. B.: The relation of albumin to precipitable iodine of serum, 107
PETIT, D. W., *see* STARR, P., 330*

PINCUS, I. J.: A hyperglycemic factor extracted from the pancreas, 669†
PINCUS, J. B.; NATELSON, S., and LUGOVOY, J. K.: Response of citric acid levels to oral administration of glucose. II. Abnormalities observed in the diabetic and convulsive state, 400
PINTO VIÉGAS, A., *see* VIÉGAS, A. PINTO
PLASS, J. B.: (Letter to the Editor) Hypersensitivity to pitressin, 650*
PODORE, C. J., *see* MIRSKY, I. A., 395
POLLACK, E., *see* MUSSIO FOURNIER, J. C., 555*
POLLEY, J. R., *see* FRIEDMAN, S. M., 109
POPPEN, J. L., *see* HURXTHAL, L. M., 126*
POSNER, C.: The effect of testosterone propionate in a case of pituitary tumor observed for nine years, 372*
POTTNER, M. M., *see* SAMUELS, L. T., 674†
POU DE SANTIAGO, A., *see* MUSSIO FOURNIER, J. C., 285*
POWER, M. H., *see* ALBERT, A., 1392*
——, *see* HAMILTON, C. F., 828*
——, *see* RALL, J. E., 1379*
——, *see* SPRAGUE, R. G., 672†
PRESTON, F. W.; TAYLOR, S. G., III, and CRUMRINE, J. L.: The effect of testosterone propionate on metastases to bone from carcinoma of the breast, 1314*
PRUNTY, F. T. G., *see* THORN, G. W., 109

QUIMBY, E. H., *see* WERNER, S. C., 342*, 664†

RAAB, W. and SMITHWICK, R. H.: Pheochromocytoma with hypothalamic manifestations and excessive hypermetabolism, 782*
RAKOFF, A. E. and FRIED, P. H.: The hormonal pattern in pseudocyesis, 668†
——, *see* LEATHEM, J. H., 654†
RALL, J. E.; KEATING, F. R., JR.; POWER, M. H., and BENNETT, W. A.: The distribution of radioiodine in a patient with metastatic adenocarcinoma of the thyroid: report of a case, 1379*
——, *see* ALBERT, A., 1392*
RALLI, E. P.; LESLIE, S.; STUECK, G. H., JR.; DUMM, M. E., and LAKEN, B.: Studies on an anti-diuretic, non chloruretic substance extracted from urines of normal and cirrhotic subjects, 652†
——, *see* DUMM, M. E., 678†
——, *see* LESLIE, S. H., 682†
RAMEY, P. M., *see* SCOTT, A. C., Jr., 1048*
RANDALL, L. M., *see* GASTINEAU, C. F., 615*
RAPAPORT, E., *see* MARGEN, S., 662†
RAWSON, R. W., *see* MCARTHUR, J. W., 299
——, *see* TRUNNELL, J. B., 1138*
REED, E., *see* MCCLENDON, J. F., 680†
REED, J. A.: Statistical analysis of deaths from diabetes in the District of Columbia for a period of 42 years—1903–1944 inclusive. Preliminary report and analysis: a comparison of two five-year periods, 1903–1907 and 1940–1944, 396
REFORZO-MEMBRIVES, J.; TRABUCCO, A., and ESCARDÓ, F.: A case of rudimentary testes, delayed growth and congenital malformations (Turner's syndrome in a male), 1333*
REIFENSTEIN, E. C., JR., *see* FOURMAN, P., 660†
REISS, R. S.; FORSHAM, P. H., and THORN, G. W.: Studies on the interrelationship of adrenal and thyroid function, 659†
——, *see* FORSHAM, P. H., 660†
REVENO, W. S.: Treatment of postoperative hyperthyroidism with antithyroid drugs 1054*
RICHARDS, C. E.; BRADY, R. O., and RIGGS, D. S.: Thyroid hormone-like properties of tetrabromthyronine and tetrachlorthyronine, 1107*
——; BROCKHURST, R. J., and COLEMAN, T. H.: Thiocyanate goiter with myxedema. Report of two cases, 446*
RIGGS, D. S., *see* PERLMUTTER, M., 430*
——, *see* RICHARDS, C. E., 1107*
RIPSTEIN, M. P., *see* VENNING, E. H., 659†
ROBBINS, C. L. and MAN, E. B.: Absorption and clinical effect of a large single dose of thyroid globulin, 377*
ROBERTIS, E. DE: Proteolytic activity in the physiology, pathology and therapeutics of the thyroid gland, 298
ROCHE, M.; HILLS, A. G., and THORN, G. W.: The level of circulating eosinophils as an indicator of adrenal cortical adequacy following major surgery, 662†
——, *see* FORSHAM, P. H., 660†
ROGERS, W. F., JR., *see* WILLIAMS, R. H., 801*
ROOT, H. F., *see* MILLARD, E. B., 394
ROSENBERG, E. F., *see* WOLFSON, W. Q., 497*, 749*
ROSSMAN, I., *see* SEIDLIN, S. M., 1122*
ROTH, P., *see* DUMM, M. E., 678†

SALTER, W. T.; KARANDIKAR, G., and BLOCK, P.: Organic and inorganic iodine, their reciprocal metabolic fates, 1080*
SAMUELS, L. T.; LEVEDAHL, B. H.; HELMREICH, M. L., and POTTNER, M. M.: Synthesis of testosterone from androstenedione-3,17 by testis tissue, 674†
——, *see* SAYERS, G., 593*
——, *see* WEST, C. D., 665†
SANTIAGO, A. POU DE, *see* POU DE SANTIAGO, A.

SAYERS, G.: Recipient of the 1949 Ciba award of the Association for the Study of Internal Secretions, 685
——: Adequacy of pituitary adrenocorticotropic function in nutritional deficiencies, 656†
——; BURNS, T. W.; TYLER, F. H.; JAGER, B. V.; SCHWARTZ, T. B.; SMITH, E. L.; SAMUELS, L. T., and DAVENPORT, H. W.: Metabolic actions and fate of intravenously administered adrenocorticotropic hormone in man, 593*
SCHMIDT, C., *see* WERNER, S. C., 342*
SCHNEEBERG, N. G.: (Letter to the Editor) Glucose tolerance in osteitis deformans, 907*
SCHNEIDER, R. W., *see* MCCULLAGH, E. P., 107
SCHORR, S., *see* ULLMANN, T. D., 401
SCHROEDER, H. A., *see* GOLDMAN, M. L., 622*
SCHROEDER, M. S., *see* GUTERMAN, H. S., 479
SCHULMAN, J., JR. and KEATING, R. P.: Metabolism and distribution of thiourea in the rat as measured with radioactive sulfur, 664†
SCHWARTZ, T. B., *see* SAYERS, G., 593*
SCHWARTZMAN, J.; CRUSIUS, M. E., and BEIRNE, D. P.: Diabetes mellitus in infants under one year of age: report of a case and review of the literature, 396
SCHWEITZER, F. L. and BAS, J. A.: Evaluation and differentiation of the various gonadotropic hormones by their action on the male toad, 297
SCOTT, A. C., JR. and RAMEY, P. M.: Total thyroidectomy in the management of diffuse toxic goiter, 1048*
SCOTT, W. W., *see* BERTHRONG, M., 579*
SCUDDER, S. T., *see* CRAMPTON, J. H., 245*
SEARLE, W. N.; HAINES, M., and BAKER, J. K.: Virilizing tumours of the ovary, 112
SEED, J. C., *see* CALKINS, E., 651†
SEED, L.: Mediastinal emphysema and pneumothorax following thyroidectomy. Report of two cases, 987*
SEGALOFF, A.: The relative effectiveness of desoxycorticosterone acetate in oil solution and in pellets diluted with cholesterol, 677†
——: (Letter to the Editor) Ethinyl estradiol, 573*
——; WEED, J. C.; STERNBERG, W. H., and PARSON, W.: The progesterone therapy of human uterine leiomyomas, 1273*
——, *see* COPPEDGE, R. L., 653†
SEIDLIN, S. M.; ROSSMAN, I.; OSHRY, E., and SIEGEL, E.: Radioiodine therapy of metastases from carcinoma of the thyroid; a six-year progress report, 1122*
SELYE, H.: The alarm reaction and the diseases of adaptation, 479
SEMMONS, E. M. and MCHENRY, E. W.: Urinary pregnanediol determination as a test of pregnancy, 852*
——, *see* MCHENRY, E. W., 399
SEVRINGHAUS, E. L.: Use of estrogens in medicine, 480
SHEARMAN, A. M., *see* WEISSBERG, J., 673†, 1259*
SIEGEL, E., *see* SEIDLIN, S. M., 1122*
SIGNOROTTI, B. T., *see* KINSELL, L. W., 671†
SIMPSON, S. L.: Addison's disease and diabetes mellitus in three patients, 403*
SINGER, B., *see* MCINTOSH, H. W., 661†
SIRI, J. J. LUSSICH, *see* LUSSICH SIRI, J. J.
SKANSE, B., *see* DOBYNS, B. M., 1171*
SLAUGHTER, D. P., *see* COLE, W. H., 1007*
SLESSOR, A., *see* BENNETT, L. L., 675†
——, *see* FORSHAM, P. H., 660†
SMITH, E. L., *see* SAYERS, G., 593*
SMITHWICK, R. H., *see* RAAB, W., 782*
SOLEY, M. H.; MILLER, E. R., and FOREMAN, N.: Graves' disease: treatment with radioiodine (I^{131}), 29*
SPEERT, H.: Ovarian granulosa cell tumor and acromegaly, 630*
SPRAGUE, R. G.; HAYLES, A. B.; MASON, H. L.; POWER, M. H., and BENNETT, W. A.: "Steroid diabetes" associated with Cushing's syndrome and excretion of 17-hydroxycorticosterone (compound F) in urine; metabolic studies, 672†
——, *see* MASON, H. L., 478
——, *see* MCARTHUR, J. W., 672†
STAFFIERI, J. J.; CAMES, O., and CID, J. M.: Corticoadrenal tumor with hypoglycemic syndrome, goiter, gynecomastia and hepatosplenomegaly, 255*
STALLWORTHY, J.: Facts and fantasy in the study of female infertility, 112
STANLEY, M. M.: First honorable mention for the 1949 Van Meter prize award of the American Goiter Association, 687
——: The direct estimation of the rate of thyroid hormone formation in man. The effect of the iodide ion on thyroid iodine utilization, 941*
STARR, P.; PETIT, D. W.; MEISTER, L., and STIRRETT, R. L.: Therapeutic studies in hyperthyroidism: propylthiouracil, 330*
STEIN, H. J.; BADER, R. A.; ELIOT, J. W., and BASS, D. E.: Hormonal alterations in men exposed to heat and cold stress, 529*
STERNBERG, W. H., *see* SEGALOFF, A., 1273*
STIRRETT, R. L., *see* STARR, P., 330*
STONE, G. C. H., *see* GOLDZIEHER, J. W., 95*, 368*

STONE, H. H.; FRANKEL, J. J., and BAKER, L. A.: Generalized insulin allergy, 895*
STRAN, H. M., *see* JONES, G. E. S., 743*
STUART, H. C.: Physical growth during adolescence, 400
STUECK, G. H., JR., *see* RALLI, E. P., 652†
SUITER, L. E., *see* MARGEN, S., 662†
SULMAN, F., *see* ZONDEK, B., 402
SUTPHIN, A., *see* ELRICK, H., 665†
SWANK, R. L. and BERGNER, G. E.: A study of the human myogram. A study of normals, and of patients with Addison's disease, thyrotoxicosis and progressive muscular atrophy, 401
SWENSON, R. E.; *see* CONNOR, A. C., 1185*

TAGNON, R., *see* WILLIAMS, R. H., 801*
TALBOT, T. R., JR. and ESCHER, G. C.: The effects of testosterone propionate on the peripheral blood and bone marrow of women with advanced inoperable carcinoma of the breast. Preliminary report, 666†
TAYLOR, H. M., *see* TEABAEUT, R., 663†
TAYLOR, S. G., III, *see* PRESTON, F. W., 1314*
TEABEAUT, R.; ENGEL, F. L., and TAYLOR, H. M.: Hypokalemic alkalosis in Cushing's syndrome. Observations on the effects of potassium chloride and testosterone propionate therapy, 663†
TEILUM, G.: Estrogen-producing Sertoli cell tumors (androblastoma tubulare lipoides) of the human testis and ovary. Homologous ovarian and testicular tumors. III, 301*
THANNHAUSER, S. J.: (Letter to the Editor) Hypoglycemia in the early phase of adrenocortical carcinoma, 791*
THOMPSON, K. W.: (Letter to the Editor) Ethinyl estradiol, 574
THOMPSON, P. K., *see* THOMPSON, W. O., 300
THOMPSON, V. T., *see* MARGEN, S., 662†
——, *see* KINSELL, L. W., 671†
THOMPSON, W. O.; THOMPSON, P. K., and MANDERNACH, D. M.: Further observations on thiouracil and related substances in the treatment of toxic goiter, 300
THORN, G. W.; FORSHAM, P. H.; PRUNTY, F. T. G., and HILLS, A. G.: A test for adrenal cortical insufficiency, 109
——, *see* BENNETT, L. L., 675†
——, *see* FORSHAM, P. H., 660†
——, *see* REISS, R. S., 659†
——, *see* ROCHE, M., 662†
TILLOTSON, K. J., *see* ALTSCHULE, M. D., 440*, 548*
TIPTON, S. R. and COLVIN, F. M.: The effects of vitamin B, thyroid, and adrenal alterations on the amino acid oxidase activity of rat liver and kidney, 684†
TOBIAN, L., JR.: Cortical steroid excretion in edema of pregnancy, pre-eclampsia, and essential hypertension, 319*
—— and JOSEPH, H.: Adrenal cortex activity in essential hypertension, 677†
TOWERY, B. T., *see* WILLIAMS, R. H., 801*
TRABUCCO, A., *see* REFORZO-MEMBRIVES, J., 1333*
TRUNNELL, J. B.; MARINELLI, L. D.; DUFFY, B.J.; HILL, R.; PEACOCK, W., and RAWSON, R. W.: Treatment of metastatic thyroid cancer with radioactive iodine: credits and debits, 1138*
TUCKER, H. ST. G., JR., *see* ALEXANDER, S. B., 862*
TURNER, H. H., *see* BELLER, C., 666†
TURNER, L., *see* WOLFSON, W. Q., 497*
TUYNMAN, P. E. and WILHELM, S. K.: Potassium deficiency associated with diabetic acidosis, 397
TWOMBLY, G. H.; MCCLINTOCK, L., and ENGELMAN, M.: Tissue localization and excretion routes of radioactive dibromestrone, 112
TYLER, E. T.; PAYNE, S., and KIRSCH, H.: Pregnenolone in male infertility, 480
TYLER, F. H., *see* SAYERS, G., 593*

ULLMANN, T. D. and SCHORR, S.: Renal dwarfism with hyperparathyroidism in a case of congenital malformation of the kidneys, 401

VAN BRUGGEN, J. T.: A comparison of methods used for the hydrolysis of conjugated urinary estrogens, 480
VARGAS, L. and KOREF, O.: Retarded absorption of pellets of protamine-zinc insulin, 818*
VENNING, E. H.; RIPSTEIN, M. P., and KAZMIN, V. E.: Urinary corticoids, 659†
——, *see* WAUGH, D., 486*
VIÉGAS, A. PINTO: Hemosedimentation test in obesity, 683†
VILANOVA, X. and CAÑADELL, J. M.: Myxedema circumscriptum thyrotoxicum. Report of two cases and remarks on its pathogenesis and treatment, 883*
VILLAVERDE, M.: The use of bismuth salts in the treatment of sporadic goiters, 462*
——: Sex hormones and staphylococcus infections, 680†
VERZAR, F. and WENNER, V.: The influence *in vitro* of desoxycorticosterone on glycogen formation in muscle, 397
VOGEL, M.; MCGAVACK, T. H., and MELLOW, J.: Effects of various estrogenic preparations on the vaginal mucosa, 480

VOGEL, W. C., *see* CONN, J. W., 656†
VRIES, A. DE and ALEXANDER, B.: Studies on amino acid metabolism. II. Blood glycine and total amino acids in various pathological conditions, with observations on the effects of intravenously administered glycine, 398

WACHMAN, J., *see* MIRSKY, I. A., 395
WALSH, G. C.; HOFFMAN, M. M.; MCALPINE, H. T., and MASON, E. H.: The metabolism of glucose and galactose when administered simultaneously to man, 670†
WARD, R.: When is malignant goiter malignant?, 1031*
WATERHOUSE, C. and KEUTMANN, E. H.: Kidney function in adrenal insufficiency, 109
WATSON, B. A.: Porphyria stimulating anorexia nervosa, 683†
WAUGH, D.; VENNING, E. H., and MCEACHERN, D.: Sympathicotropic (Leydig) cell tumor of the ovary with virilism. Report of a case, 486*
WEED, J. C., *see* SEGALOFF, A., 1273*
WEISSBERG, J.; MCGAVACK, T. H.; SHEARMAN, A. M., and DREKTER, I. J.: Behavior of electrolytes during treatment of diabetic keto-acidosis, 673†
WEISSBERG, J.; MCGAVACK, T. H.; SHEARMAN, A. M., and DREKTER, L. J.: Electrolyte balance in uncontrolled and controlled diabetic ketosis and acidosis, 1259*
WENNER, V., *see* VERZAR, F., 397
WERNER, S. C.; GOODWIN, L. D., and QUIMBY, E. H.: The tracer technique with radioiodine I^{131} as a potential substitute for the basal metabolic rate determination in routine clinical practice, 664†
——; QUIMBY, E. H., and SCHMIDT, C.: The use of tracer doses of radioactive iodine, I^{131}, in the study of normal and disordered thyroid function in man, 342*
WEST, C. D. and SAMUELS, L. T.: The distribution and metabolism of circulating testosterone, 665†
WEST, R. M., *see* GREENBLATT, R. B., 668†
WHEELER, M. L., *see* FORBES, A. P., 680†
WHITESELL, F. B., JR. and BLACK, B. M.: A statistical study of the clinical significance of lymphocytic and fibrocytic replacements in the hyperplastic thyroid gland, 1202*
WILHELM, S. K., *see* TUYNMAN, P. E., 397
WILKERSON, H. L. C. and HEFTMANN, E.: Screening method for blood glucose, 397
WILLIAMS, M. M. D., *see* ALBERT, A., 1392*
WILLIAMS, R. H.: An evaluation of newer methods of treatment of thyrotoxicosis, 300
—— and KAY, G. A.: Further studies on the correlation of chemical structure and antithyroid effect, 107
——; TOWERY, B. T.; ROGERS, W. F., JR.; TAGNON, R., and JAFFE, H.: The antithyroid action of 5-iodothiouracil, 6-methyl-5-iodothiouracil, thiocytosine and (Ca) 4-n-propyl-6-oxypyrimidyl-2-mercaptoacetic acid, 801*
WILSON, D. L.: Recipient of the 1949 Schering fellowship of the Association for the Study of Internal Secretions, 686
WINSAUER, H. J. and MANNING, J. C., JR.: A masculinizing tumor of the ovary in a postmenopausal woman, 774*
WOLFSON, W. Q.; GUTERMAN, H. S.; LEVINE, R.; COHN, C.; HUNT, H. D., and ROSENBERG, E. F., with the technical assistance of KADOTA, K. and TURNER, L.: An endocrine finding apparently characteristic of gout. Very low urinary 17-ketosteroid excretion with clinically normal androgenic function, 497*
——; HUNT, H. D.; LEVINE, R.; GUTERMAN, H. S.; COHN, C.; ROSENBERG, E. F.; HUDDLESTUN, B., and KADOTA, K.: The transport and excretion of uric acid in man. V. A sex difference in urate metabolism: with a note on clinical and laboratory findings in gouty women, 749*
——; KREVSKY, D.; LEVINE, R.; KADOTA, K., and COHN, C.: Endocrine factors in gout: the significance of differences in childhood and adult urate metabliosm, 666†
WYATT, J.: Testosterone propionate in inoperable carcinoma, 401

ZIMMERMAN, B. and DONOVAN, T. J.: Hyperglycemic effect of insulin, 398
ZONDEK, B. and BRZEZINSKI, A.: Inactivation of estrogenic hormone by women with vitamin B deficiency, 402
——; SULMAN, F., and BLACK, R.: Hormonal test for fetal death in undisturbed pregnancy, 402

SUBJECT INDEX

* Original article.

† Abstract of paper presented at the Thirty-first Annual Meeting of the Association for the Study of Internal Secretions.

Other items are abstracts of articles which appeared in current medical journals and miscellaneous entries.

ABNORMALITIES: *see* Congenital anomalies; and under various endocrine glands

ABORTION: *see* Pregnancy

ABSORPTION: *see also* Administration; and under various glandular preparations

—— retarded; of protamine-zinc insulin pellets, in normal and diabetic rabbits, 818*

ABSTRACTS

—— of current endocrine literature, 106, 297, 394, 478

—— of papers presented at Thirty-first Annual Meeting of the Association, Atlantic City, 651†

ACETIC ACID, in genesis of diabetic acidosis, 1238*

ACIDOSIS: *see* Diabetes mellitus

ACROMEGALY: *see* Pituitary disorders

ADDISON'S DISEASE: *see also* Adrenals, disorders; Steroids

—— and diabetes mellitus (autopsies), 245*, 403*

—— blood in, *see* Blood; Electrolytes

—— carbohydrate metabolism in, *see* Carbohydrate metabolism

—— development of diabetes mellitus in (autopsy), 36*

—— electrolyte metabolism in, *see* Electrolytes

—— eosinophiles in: *see* Blood, cells

—— loss of axillary and pubic hair in, in woman with regular menstration, 555*

—— myogram in, 401

—— pregnancy in; hormone and electrolyte metabolism, 514*

—— radioiodine uptake of thyroid in, 342*, 659†, 660†

—— urine in; *see* Adrenals, preparations and compounds; Steroids

THERAPY: *see also* Adrenals, preparations

—— effect of adrenal compounds on thyroid uptake of radioiodine in, 659†, 660†

—— effect of synthetic Compound E acetate on blood ketone bodies and glucose in, 675†

—— response to single injection of ACTH in, 661†

—— with Compound E (pellets), 660†

ADDISON'S DISEASE (cont.)

THERAPY (cont.)

—— with DOCA, in Addison's disease and diabetes, 36*, 245*, 403*

—— with intraoral administration of desoxycorticosterone tablets, 1324*

—— with sublingual DOCA for as long as seven years, 1324*

—— with testosterone and DOCA, 403*

ADDRESS, on the subject of Henry S. Plummer, 967*

ADMINISTRATION: *see* also substance involved

METHODS

—— buccal tablets *vs.* other methods; for estrogens, 382*

—— comparison of DOCA in oil solution and in pellets diluted with cholesterol, in rats, 677†

—— comparison of effects of Compound E by intramuscular injection or pellet implantation, 660†

—— comparison of; for estrogens, 725*, 480

—— comparison of; for progesterone, 736*

—— comparison of insulins, for successful implantation, 818*

—— intravenous administration of sex and other hormones; comparisons, 1406*, 111

—— of administration of chorionic gonadotropin; effect on excretion, 268*

—— oral *vs.* intramuscular; for ethinyl estradiol; comparison of potencies, 573*

—— oral *vs.* intravenous; for radioactive racemic thyroxine in myxedema, 1406*

—— pellet implantation; *see* substances involved, under Adrenals; Androgens; Estrogens; Insulin; Progesterone

—— tablets, for oral administration of DOCA; comparison with intramuscular route, 1324*

ADRENALS: *see also* Addison's disease; and Cushing's syndrome

—— adrenal-like masculinizing tumor of ovary, 774*

—— adrenocortical function in patients

ADRENALS (cont.)
with tumors at or near the pituitary, 1292*
—— cortical activity in essential hypertension, 677†
—— cortical adequacy, indicated by level of eosinophiles, following major surgery, 662†
—— cortical function in childhood hermaphrodism and in precocious puberty, 674†
—— cortical function; relation to gout, 497*
—— in Addison's disease associated with diabetes mellitus (autopsies), 36*, 245*, 403*
—— possible role of, in idiopathic hirsutism, 795*
—— width of cortex in lymphatic leukemia, lymphosarcoma and hyperthyroidism, 158*
DISORDERS
—— Addison's disease, *see* Addison's disease
—— adrenal cortical insufficiency; a test for; and kidney function in, 109
—— adrenogenital syndrome, urate metabolism in; effect of stilbestrol and of surgery, 749*
—— alarm reaction and diseases of adaption; relation to nephrosclerosis and hypertension, 479
—— Cushing's syndrome, *see* Cushing's syndrome
—— of medulla, *see* Adrenal disorders, tumors, (pheochromocytoma)
—— precocious puberty, *see* Puberty, precocious
—— virilism, *see* Virilism
Tumors
—— cortical carcinoma; hypoglycemia in, 791*
—— cortical carcinoma in male with excess urinary gonadotropin (autopsy), 451*
—— cortical tumors *vs.* hyperplasia, 680†
—— corticoadrenal; with hypoglycemic syndrome, goiter, gynecomastia and hepatosplenomegaly, 255*
—— pheochromocytoma; effect of antagonist to epinephrine in, 651†
—— pheochromocytoma; nor-epinephrine in, 652†
—— pheochromocytoma; tetraethylammonium bromide in diagnostic test for, 478
—— pheochromocythoma, with hypothalamic manifestations and

ADRENALS (cont.)
DISORDERS (cont.)
Tumors (cont.)
excessive hypermetabolism, 782*
—— pheochromocytomas, 108
PHYSIOLOGY
—— ACTH: *see* Pituitary, preparations
—— adrenalectomized rats, treated; role of emotional stress in survival of, 678†
—— adrenalectomy; effect on amino acid oxidase in the rat, 684†
—— adrenalectomy; response of white blood cells to, in the rat, 678†
—— adrenals of malnourished rats; effect of nonspecific stress on, 656†
—— *adrenocorticotropic hormone of the pituitary* (*ACTH*): *see* Pituitary, preparations
—— ascorbic acid of chick adrenal; inability of ACTH or epinephrine to deplete, 655†
—— cortex; possible involvement in mobilization of fat to liver, in the mouse, 657†
—— cortex; possible role in sex difference in urate metabolism, 749*
—— cortex; role in development of axillary and pubic hair, 555*
—— cortical activity in heat and cold stress; effect of ACTH on, 529*
—— cortical function; evaluation of, with single injection of ACTH, 661†
—— cortical response, as indicated by changes in circulating eosinophiles, 714*
—— function, in infants, 646*
—— secretory activity following ACTH intravenously in man, 593*
PREPARATIONS AND COMPOUNDS
—— cortical extract; stimulator of nitrogen metabolism during insulin hypoglycemia in the rat, 657†
—— cortical hormone, in blood of dogs, 658†
—— cortical hormones in regulation of ACTH activity, 656†
—— cortical steroid excretion in edema of pregnancy, pre-eclampsia and essential hypertension, 319*, 1436*
—— cortical steroid excretion in infants, 646*
—— cortical steroids; cholesterol precursor and source material, 656†
—— corticoids, urinary; comparison of chemical and biologic assay, 659†
—— corticosteroids, urinary, in diabetic acidosis, 672†
—— cortin and 17-ketosteroid excretion following sodium deprivation and

ADRENALS (cont.)
PREPARATIONS AND COMPOUNDS (cont.)
administration of DOCA, 661†
—— cortin-like substances in testicular chorioma, 615*
—— 17-hydroxycorticosterone (Compound F); isolation from urine in Cushing's syndrome associated with severe diabetes mellitus, 478
—— 11-oxysteroids and Compound F in Cushing's syndrome with "steroid diabetes," 672†
—— 11-oxysteroids; increased production of, after electroconvulsive therapy for mental disease, 548*
—— 11-oxysteroids; in remissions of mental disease following shock therapy, 440*
—— 11-oxysteroids, urinary; in adrenal cortical carcinoma, 791*
—— steroids; renal function in normal and adrenalectomized rats following, 658†
—— urinary corticoids in pregnant woman with Addison's disease, 514*
—— urinary glycogenic corticoids in virilizing Leydig cell tumor of ovary, 486*
Compound E
—— acetate and Lipoadrenal Cortex; effect on thyroid uptake of radioiodine, in Addison's disease and in panhypopituitarism, 659†, 660†
—— acetate (pellets), in the treatment of Addison's disease; physiology and biochemistry, 660†
Desoxycorticosterone (acetate)
—— and ACTH; effect on exophthalmos and fat mobilization in guinea pigs, 937*
—— and testosterone pellets in treatment of Addison's disease with diabetes; effects of overdosage, 403*
—— comparison of administration in oil solution and in pellets, in adrenalectomized rats, 677†
—— effect in hypokalemia, 691*
—— effect of single dose on electrolyte metabolism, in normal man, 660†
—— effect on adreno-demedullated rat, 656†
—— effect on carbohydrate metabolism in case of Addison's disease and diabetes mellitus, 245*
—— hypertensive effects of; potentiation by sodium salts, 109
—— in tablet form, in oral therapy of

ADRENALS (cont.)
PREPARATIONS AND COMPOUNDS (cont.)
Desoxycorticosterone (acetate) (cont.)
Addison's disease, 1324*
—— in vitro; influence on glycogen formation in muscle, 397
—— (pellets) effect on relation of fluid intake to blood pressure, in rats, 478
—— (subcutaneously and in pellets) in treatment of Addison's disease followed by diabetes mellitus, 36*
Epinephrine
—— and radioiodine; effect on thyroid uptake of iodine and on eosinophiles, in Addison's disease and in panhypopituitarism, 659†
—— content of pheochromocytoma, 782*
—— effect on adrenal cortical hormone in blood of dogs, 658†
—— inability of, to deplete ascorbic acid of chick adrenal, 655†
—— nor-epinephrine in adrenal medulla, 652†
—— piperidomethyl-benzodioxane (933-F), an antagonist of, 651†
—— response of eosinophiles to, following major surgery, 662†
AFRICAN Negro women; causes of sterility in, 111
AGE: *see also* Infants; Children; and under various endocrine disorders
—— effect on urinary excretion of 17-ketosteroids, 426*
—— in relation to Hashimoto's chronic thyroiditis, 980*
—— in relation to type of tissue replacement in hyperplastic thyroid gland, 1202*
—— relation to incidence of nonencapsulated sclerosing thyroid tumors, 1216*
—— senescence; thyroid collection of I^{131}, and serum PBI in, 430*
AGRANULOCYTOSIS: *see* Blood, cells; Thiouracil
ALKALOSIS: *see also* Electrolytes
—— hypokalemic, in Cushing's syndrome; effect of KCl and testosterone therapy, 663†
—— potassium deficiency in; a mechanism of, 676†
ALLERGY: *see also* Antihormones; and specific substance involved
—— hypersensitivity to pitressin, 650*
—— to insulin, generalized, 895*
—— to steroid hormones, 681†
ALLOXAN: *see* Diabetes mellitus
ALPHA-TOCOPHEROL: *see* Vitamins, E
AMENORRHEA: *see* Menstruation

AMERICAN CANCER SOCIETY: British American exchange fellowships in cancer research, 575
AMERICAN COLLEGE OF PHYSICIANS: fellowships for Latin-American physicians, 689
AMERICAN DIABETES ASSOCIATION
ANNUAL MEETING
—— for 1949, Atlantic City, June 1949:
— announcements of, 211, 296, 393, 472
— program of section in joint meeting with Association for the Study of Internal Secretions, 389, 470
— abstracts of papers on program, 669†
POSTGRADUATE ASSEMBLY in Endocrinology and Diabetes: (with the Association for the Study of Internal Secretions), April 1950, Miami Beach, 1242, 1438
AMERICAN GOITER ASSOCIATION
ANNUAL MEETINGS
—— Madison, Wisconsin, May 1949:
— announcements of, 105, 212, 293, 391
— program of, 293, 391
—— Houston, Texas, March 1950:
— announcements of, 794, 912, 1068, 1244, 1442
PRESIDENTIAL ADDRESS
—— for 1949, 967*
—— for 1948 (belated), 974*
VAN METER PRIZE AWARD
—— essays
— winning 1949 Van Meter Prize, 913*
— first honorable mention, 941*
— second honorable mention, 955*
—— for 1949,
— announcement of, 105
— recipient of, and honorable mentions, 687
—— for 1950
— announcement of, 912, 1068, 1244, 1442
AMINO ACID: *see* Nitrogen
AMPHETAMINE, with diet, in the prolonged medical treatment of obesity; toxicity, 275*
ANALOGUES
—— of thiouracil; antithyroid action of, 801*
—— of thyroxine, physiologic activity of, 1099*, 1107*
—— of thyroxine; thyroxine-like and antithyroxine activity of, 955*
ANDROBLASTOMA: *see* Ovary, tumors; Testis
ANDROGENS: *see also* Gonadotropins; Hermaphrodism; Sex; Steroids; Testis
—— abnormal; relation to genetic hyperuricemia, and to gout, 749*, 666†
—— in urine; *see* Steroids
—— normal activity of, associated with low urinary 17-ketosteroids, in gout, 497*
—— stimulation of, *see* Gonadotropins
—— testosterone, circulating; distribution and metabolism of, 665†
—— testosterone; synthesis from androstenedione-3,17 by testis tissue in vitro, 674†
EFFECTS AND THERAPY
—— effect on urinary gonadotropins in castrated males, 654†
—— influence on rate of radioiodide uptake, 430*
—— intravenously injected sex and other hormones; effect on blood flow in human endometrium, 111
—— toxemia (hypercalcemic syndrome) from, in patients with osteolytic metastases, 1*
Testosterone
—— effect of, on urinary 17-ketosteroids in gout, 497*
—— effect on blood ketones and other products of fat and protein catabolism, in diabetes, 671†
—— in Cushing's syndrome, 663†
—— in staphylococcus infections, 680†
—— inability of (i.m. and pellets), to reduce urinary gonadotropin in eunuchoid men, 113*
—— methyltestosterone; spermatogenesis following administration of (linguets and ointment); coincidental neoplasm, 163*
—— new esters of; androgenic activity compared to testosterone propionate, 679†
—— pellet implantation and oral route, in therapy of Addison's disease with diabetes, 403*
—— pellets, in treatment of woman with acromegaly, 126*
—— propionate; effect in case of pituitary tumor observed nine years, 372*
—— propionate; effect of crude folic acid antagonists on seminal vesicle response to, in mice, 674†
—— propionate; effects of small doses on spermatogenesis, 666†
—— propionate; effects on blood and bone marrow of women with inoperable breast cancer, 666†

ANDROGENS (cont.)
EFFECTS AND THERAPY (cont.)
Testosterone (cont.)
—— propionate; effect on bone metastases in breast cancer, 1314*
—— propionate; effect on growth of axillary hair, measured quantitatively, 665†
—— propionate; effect on hypokalemic alkalosis in Cushing's syndrome, 663†
—— proprionate; effect on penis of castrated, hypophysectomized rat, 679†
—— propionate, in inoperable carcinoma, 401
—— propionate; local action of, on development of axillary hair in the male, 1434*
—— relation to sex difference in urate metabolism, 749*
—— spermatogenesis in eunuchoidism, following therapy with (oral, i.m. and pellets), 1245*
ANEMIA: *see* Blood, cells
ANESTHESIA, with pentothal; basal metabolism testing under, 1190*
ANGINA PECTORIS: *see* Heart
ANNOUNCEMENTS: *see* Association; and American Cancer Society; American College of Physicians; American Diabetes Association; American Goiter Association; Jefferson Medical College; Kellogg Foundation; Laurentian Hormone Conference; National Research Council; University of California Medical School; University of Georgia School of Medicine
ANNUAL MEETINGS: *see* Announcements
ANOMALIES: *see* Congenital anomalies; and abnormalities under various endocrine glands
ANOREXIA NERVOSA:
—— radioiodine uptake of thyroid in, 342*
—— simulated by porphyria, 683†
ANTIBODIES, uninfluenced by ACTH intravenously, 593*
ANTIHISTAMINIC DRUGS: *see also* Allergy
—— in treatment of allergy to insulin, 895*
—— in treatment of hypersensitivity to pitressin, 650*
ANTIHORMONES: *see also* Antibodies; Antithyroid drugs
—— antidiuretic hormone *see also* Pituitary, preparations
—— antidiuretic nonchloruretic substance extracted from urine, 652†
ANTIHORMONES (cont.)
—— antigonadotropin formation in man, 654†
—— antihormone formation complicating treatment of infertile men, 213*
—— antihormone formation during chorionic gonadotropin therapy, 384*
—— antihormones; properties of, 213*
—— antihormones to pituitary gonadotropin; effect on sperm, testis and urinary gonadotropins, 355*
—— anti-insulin: *see* Insulin
ANTITHYROID DRUGS: *see also* Iodine; Thiouracil; Thyroid
—— action of, studied by radioiodine, 171*
—— antithyroid effect of; further studies on the correlation of chemical structure with, 107
—— in preoperative treatment of hyperthyroidism; favorable and unfavorable effects, 999*
—— tetrabrom- and tetrachlorthyronine, 1099*, 1107*
—— thiocyanate goiter with myxedema, 446*
—— thiooxazolidone and the pathogenesis of simple goiter, 1069*
—— thiouracil and compounds, *see* Thiouracil
—— thyronine compounds; antithyroxine activity of, 955*
ANTIVITAMINS: *see also* Vitamins
—— antagonists to crude folic acid; effect on response to testosterone in mice, 674†
AORTA: *see* Vascular system
ARRHENOBLASTOMA: *see* Ovary, tumors
ARTERIES: *see* Vascular system
ARTHRITIS: *see also* Gout
—— effect of roentgenotherapy on 17-ketosteroid excretion in ankylosing spondylarthritis, 79*
—— rheumatoid, and spondylitis in males; urinary 17-ketosteroids in, 497*
ASCHHEIM-ZONDEK TEST: *see also* Gonadotropins; Pregnancy; Tests
—— in precocious puberty, associated with ovarian dysgerminoma, 1349*
ASCORBIC ACID: *see* Adrenals; Methods; Vitamins
ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS
ABSTRACTS
—— of current endocrine literature, 106, 297, 394, 478
—— of papers presented at Thirty-first Annual Meeting, 651†

ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS (cont.)
ANNUAL MEETINGS
—— Thirty-first, Atlantic City, New Jersey, June 1949:
— announcements of, 103, 211, 292, 386
— program of (last session joint, with American Diabetes Association), 386, 467
— abstracts of papers on program, 651†
—— Thirty-second, San Francisco, California, June 1950:
— announcements of, 792, 909, 1065, 1241, 1439
AWARDS AND FELLOWSHIPS
(Ciba award; Squibb award; Ayerst, McKenna & Harrison fellowship; Schering fellowship):
—— for 1949:
— announcement of, 103
— recipients of, 685
—— for 1950:
— announcements of, 793, 910, 1066, 1242, 1440
EDITORIALS, 1238, 1429
FELLOWSHIPS: *see* Association, awards
LETTERS TO THE EDITOR, 382*, 384*, 385*, 573*, 574*, 650*, 791*, 907*, 1432*, 1434*, 1436*
OFFICERS; COUNCIL, COMMITTEE, AND EDITORIAL BOARD MEMBERS
—— for *1948–49:* *see* general information page, front ad section, January–June issues
—— for *1949–50:* *see* Ibid., July–December issues
POSTGRADUATE ASSEMBLIES IN ENDOCRINOLOGY
—— February 1949, Oklahoma City: announcement, and preliminary program of, 101
—— April 1950, Miami Beach (with American Diabetes Association): announcements of, 1240, 1438
ROSTER, new; request for biographical data for, 792, 909, 1065
AURICULAR FIBRILLATION: *see* Heart
AUTHOR INDEX to Volume 9 (1949), 1443
AWARDS: (including Fellowships and Grants): *see* Association, awards; American Cancer Society; American College of Physicians; American Goiter Association; Jefferson Medical College; Kellogg Foundation; and National Research Council
AYERST, McKENNA & HARRISON FELLOWSHIP: *see* Association, awards
AZOOSPERMIA: *see* Testis, spermatozoa

BASAL METABOLISM: *see also* Iodine; Thiouracil; Thyroid
—— excessive hypermetabolism in pheochromocytoma with hypothalamic manifestations; effect of removal of tumor, 782*
—— in heat and cold stress in men, 529*
—— in routine clinical practice; substitution of tracer technique with I^{131} for, 664†
—— relation to protein-bound blood iodine, 1185*
—— relation to type of parenchymal replacement in hyperplastic thyroid gland, 1202*
—— testing, under pentothal anesthesia, 1190*
BENADRYL: *see* Antihistaminic drugs
BENZODIOXANE: effects in pheochromocytoma, 651†, 108
BETA RAY counting, in measurement of urinary I^{131}, 841*
BICARBONATE: *see* Carbon, dioxide
BIOGRAPHY of Henry S. Plummer, 967*
BISMUTH salts, in treatment of sporadic goiters, 462*
BLOOD: *see also* under constituent or under endocrine disorder involved
—— alpha-tocopherol in, before and during treatment, 743*
—— bicarbonate and chloride, in hypokalemia, 691*
—— citric acid, after oral glucose, in diabetes, 400
—— ketone bodies; effect of Compound E acetate (synthetic) on, in Addison's disease, 675†
—— ketones; effect of testosterone on in diabetes with thyrotoxicosis, 671†
—— lipids, in tumors at or near the pituitary, 1292*
—— lymphatic leukemia; width of adrenal cortex in, 158*
——pepsidases; effect of ACTH on, in man, 593*
—— pressure, *see* Vascular system
—— urate metabolism, 749*
—— urea nitrogen, in hypercalcemic syndrome, 1*
—— uric acid; hereditary hyperuricemia, relation to gout, 666†
—— uric acid; idiopathic hyperuricemia, urinary 17-ketosteroids in, 497*
—— vessels, *see* Vascular system
CALCIUM
—— calcium, phosphorus, cholesterol and protein, in pseudohypoparathyroidism, 862*
—— hypercalcemia in breast cancer with bone metastases; effect of

BLOOD (cont.)
CALCIUM (cont.)
androgen therapy, 1314*
—— hypercalcemic syndrome associated with androgenic and estrogenic therapy, 1*
—— spontaneous hypocalcemia and electrocerebral dysfunction, 398
CELLS
—— anemia of hypophysectomized rats; effect of nonendocrine hemopoietic agents on, 676†
—— effect of radioiodine therapy on, 1138*
—— eosinophiles and leukocytes, during menstrual cycle and reproduction, 714*
—— eosinophiles and lymphocytes during heat, cold and exercise; effect of ACTH on, 529*
—— eosinophiles as indicator of adrenal cortical adequacy following major surgery, 662†
—— eosinophiles; decrease in, after electrically induced convulsions, and after ACTH, 440*
—— eosinophiles; effect of ACTH on, 109
—— eosinophiles; effect of Compound E on, in Addison's disease, 660†
—— eosinophiles; effect of single injection of ACTH on, in normal subjects and in those with Addison's disease and with pituitary tumor, 661†
—— eosinophiles; effect of testosterone with ACTH on, in Cushing's syndrome, 663†
—— eosinophiles; effect of withdrawal of insulin on, in diabetes, 672†
—— eosinophiles following administration of epinephrine and radioiodine, in Addison's disease and in panhypopituitarism, 659†
—— eosinophiles, in essential hypertension, 677†
—— eosinophiles, lymphocytes, and neutrophiles, following ACTH intravenously, 593*
—— granulopenia during propylthiouracil therapy, 330*
—— hemosedimentation test in obesity, 683†
—— red; effect of testosterone on, in therapy of breast cancer, 666†
—— white; response to adrenalectomy, stress and pantothenic acid, in the rat, 678†
CHOLESTEROL
—— cholesterol and arterial intima in the rat; effect of propylthiouracil and cholesterol on, 106
—— cholesterol (free and ester) in normal men, before and after ACTH, 656†
—— cholesterol, in Hashimoto's disease, 980*
—— cholesterol, in tumors at or near pituitary, 1292*
HORMONES
—— adrenal cortical hormone in, in dogs, 658†
—— antihormones, *see* Antihormones
—— free thyroxine in, 149*
—— important source of material for synthesis of cortical steroids, 656†
—— TSH and thyroxine in, 653†
IODINE: *see also* Iodine; Thiouracil; Thyroid
—— in study of labeled iodocasein in myxedema, 828*
—— nomenclature of fractions; "spurious" *vs.* hormonal iodine in, 1080*
—— precipitable; relation of serum albumin to, 107
—— protein-bound; effect of propylthiouracil on, 330*
—— protein-bound; effect of radioiodine therapy on, in Graves' disease, 29*
—— protein-bound; effect of tetrabrom- and tetrachlorthyronine on, 1099*, 1107*
—— protein-bound, following large single dose of thyroid globulin, 377*
—— protein-bound; in hyperthyroidism following radioiodine therapy of thyroid metastases, 1138*
—— protein-bound; in myxedema, following administration of labeled iodide, thyroglobulin and thyroxine, 1392*
—— protein-bound; in senescence, hypothyroidism and hypopituitarism, 430*
—— protein-bound, in thiocyanate goiter with myxedema, 446*
—— protein-bound, labeled and unlabeled, following labeled racemic thyroxine therapy in myxedema, 1406*
—— protein-bound, or serum precipitable; constancy of, in healthy adults, 768*
—— protein-bound; simplified method for determination of; clinical application, and relation to B.M.R., 1185*

BLOOD (cont.)
IODINE (cont.)
—— radioactive, in direct estimation of rate of thyroid hormone formation in man; calculation of serum iodide from, 941*
—— radioactive, in serum, urine and expired air, in treated thyroid carcinoma, 1080*
—— radioactive, in treated metastatic adenocarcinoma of the thyroid, 1379*
—— radioactive, protein-bound; in various thyroidal states, 171*
—— serum precipitable; concentrations during pregnancy, 299
—— serum-precipitable; low, in tumors at or near the pituitary, 1292*
PHOSPHORUS
—— alkaline phosphatase; relation to carbohydrate metabolism in dogs, 907*
—— in acromegaly, 126*
—— in diabetic keto-acidosis, 673†
—— in hypercalcemic syndrome, 1*
—— phosphate; decreased, in diabetic ketosis treated with insulin, 1245*
POTASSIUM
—— effects of therapy on, in Addison's disease and diabetes, 403*
—— hypokalemia, 691*
—— hypokalemic alkalosis in Cushing's syndrome; effect of KCl and testosterone on, 663†
—— hypopotassemia in diabetic keto-acidosis, 673†
—— marked decrease in, during insulin therapy of diabetic ketosis, 1245*
SUGAR: *see also* Carbohydrate; Diabetes mellitus; Insulin
—— a simple bedside method for the estimation of, 394
—— effect of Compound E acetate on, in Addison's disease, 675†
—— effect of Compound E on, in Addison's disease, 660†
—— effect of PZ-insulin implantation on, in normal and diabetic rabbits, 818*
—— glucose; screening method for, 397
—— glucose tolerance curves in osteitis deformans, 907*
—— glucose tolerance test, in decerebrate rats, 670†
—— glucose tolerance test in diabetes mellitus following Addison's disease, 36*
—— glucose tolerance test, in masculinizing tumor of ovary, 774*
—— glucose tolerance test in tumors at or near the pituitary, 1292*
—— hyperglycemia; metabolism of glucose and galactose, in study of, 670†
—— hyperglycemic effect of insulin, 398
—— hyperglycemic factor extracted from pancreas, 669†
—— hypoglycemia in diabetes mellitus with Addison's disease, 403*
—— hypoglycemia in early adrenocortical carcinoma, 791*
—— hypoglycemia in insulin shock therapy; gastric secretory response to, 394
—— hypoglycemia response to insulin in Turner's syndrome in a male, 1333*
—— hypoglycemic syndrome, with corticoadrenal tumor, 255*
—— in Addison's disease combined with diabetes mellitus, 245*
—— in diabetics with generalized allergy to insulin, 895*
—— in the management of diabetes mellitus, 395
—— insulin hypoglycemia in rat; stimulation of nitrogen metabolism during, 657†
—— relation to serum potassium and other electrolytes, during insulin therapy of diabetic ketosis, 1245*
BODY GROWTH AND WEIGHT: *see* Children; Dwarfism; Infants; Nutrition; Obesity, Pituitary, growth hormone
BODY TEMPERATURE: *see* Temperature
BONES
—— abnormal digits, associated with coarctation of aorta, hypo-ovarianism and dwarfism, 622*
—— changes in acromegaly, 126*
—— closure of epiphyses following androgen therapy in 24-year-old male with pituitary tumor, 372*
—— hypertrophic pulmonary osteoarthropathy; pituitary implications in, 297
—— in pseudohypoparathyroidism, 862*, 665†
—— in Turner's syndrome in a male, 1333*
—— marrow changes, following radioiodine therapy, 1138*
—— marrow; effect of testosterone on cells of, in therapy of breast cancer, 666†
—— metastases to, from breast cancer; effect of testosterone on, 1314*
—— metastases to, from thyroid cancer; radioiodine therapy of, 1122*, 1138*
—— metastases to, from thyroid cancer;

BONES (cont.)
study of function, with radioautography, 1153*
—— ossification of, in precocious puberty associated with ovarian dysgerminoma, 1349*
—— osteitis deformans; glucose tolerance curves in, 907*
—— osteitis deformans; insulin for relief of pain in, 385*
—— osteolytic metastases; hypercalcemic syndrome associated with sex hormone therapy in, 1*
—— radioiodine content of red marrow and of metastases, 56 hours after oral ingestion of I^{131} for thyroid cancer, 1379*
BOOKS RECEIVED, 474
BRAIN: *see also* Emotion; Mental disease; Psychoneurosis; Nervous system; Pituitary
—— decerebrate rats; carbohydrate metabolism in 670†
—— electrocerebral dysfunction and spontaneous hypocalcemia, 398
—— electroencephalogram; effect of Compound E on, in Addison's disease, 660†
—— electroencephalogram in Turner's syndrome in the male, 1333*
—— encephalogram in pheochromocytoma with hypothalamic manifestations, 782*
BREAST
—— cancer; androgenic and estrogenic therapy of; hypercalcemic syndrome associated with, 1*
—— carcinoma, inoperable; effects of testosterone on peripheral blood and on bone marrow in, 666†
—— carcinoma; metastases to bone; effect of testerone propionate on, 1314*
—— during progesterone therapy of uterine leiomyomas, 1273*
—— in 8-year-old girl with ovarian dysgerminoma, 1349*
—— lactation, cessation of; effect on hyperthyroidism, 330*
—— persistent lactation in acromegaly, 126*
—— prolactin; assay of, in breast carcinoma, chronic cystic mastitis and other endocrine disorders, 653†
GYNECOMASTIA
—— associated with corticoadrenal tumor, 255*, 791*
—— associated with feminizing androblastoma testis, 301*
—— enlargement of nipples in male dog with feminizing testicular tumor, 579*
BREAST (cont.)
GYNECOMASTIA (cont.)
—— in paraplegic males 457*
BRITISH AMERICAN EXCHANGE FELLOWSHIPS in cancer research, awarded by the American Cancer Society, 575
BROMINE
—— replacing iodine in thyroxine; effect, 1099*, 1107*
—— sodium bromide, unable to inhibit iodine-deficient goiter, in rats, 1107*
—— tetraethylammonium bromide, in diagnosis of pheochromocytoma, 478

CALCIUM METABOLISM: *see also* Blood, calcium; Bones; Electrolytes; Parathyroids
—— calcium balance in Cushing's syndrome with "steroid diabetes," 672†
—— calcium retention correlated with potassium loss, following single dose of DOCA, 660†
—— hypercalcemia in breast cancer with bone metastases; effect of androgen therapy on, 1314*
—— hypercalcemic syndrome associated with androgenic and estrogenic therapy, 1*
—— in pseudohypoparathyroidism, 862*, 665†
—— recalcification of osteolytic and decalcification of osteoplastic metastases to bone from breast cancer, during androgen therapy, 1314*
—— spontaneous hypocalcemia and electrocerebral dysfunction, 398
CANCER: *see also* under various organs involved; and under Tumors
—— destruction of metastasis of thyroid cancer, treated with radioiodine, 1122*, 1138*
—— incidence of, in endocrine case histories, 682†
CARBOHYDRATE METABOLISM: *see also* Adrenals; Blood, sugar; Diabetes mellitus; Insulin
—— citric acid response to oral glucose; abnormalities in diabetes, 400
—— dextrose tolerance test: *see* Blood, sugar
—— effect of implanted PZ insulin on, in normal and diabetic rabbits, 818*
—— following ACTH intravenously, 593*
—— glucose and galactose administered simultaneously; metabolism of, in man, 670†
—— glucose tolerance test: *see* Blood, sugar
—— glycine and total amino acids in various pathologic conditions, 398

CARBOHYDRATE METABOLISM (cont.)
—— glycogen formation in muscle; influence *in vitro* of desoxycorticosterone on, 397
—— glycogen in vaginal smear; limitations as an index of estrogen activity, 1359*
—— hyperglycemia: *see* Blood, sugar
—— hypoglycemia: *see* Blood, sugar
—— in decerebrate rats, 670†
—— in diabetes mellitus and Addison's disease, 245*, 403*
—— in diabetics with generalized allergy to insulin, 895*
—— in masculinizing tumor of ovary, 774*
—— in pregnant woman with Addison's disease, 514*
—— insulin tolerance test: *see* Insulin
—— relation of serum alkaline phosphatase to, in dogs, 907*
—— studies in, by means of radioactive carbon, 1238*
—— sugar tolerance test, *see* Blood, sugar
—— urinary glycogenic corticoids and glucose tolerance curve, in virilizing Leydig cell tumor of ovary, 486*
CARBON
—— dioxide, in serum; high, in hypokalemia, 691*
—— dioxide, of plasma, and CO_2/Cl ratio, in essential hypertension, 677†
—— radioactive, in study of diabetes, 1238*
CARCINOMA: *see* Cancer
CASTRATION: *see* Climacteric; Menstruation; Ovary; Testis
CELLS: *see* Blood, cells; Tissues; and organ involved
CHEMISTRY: *see* Methods; Tests; and under various chemical compounds and gland preparations
CHILDREN: *see also* Dwarfism; Growth; Infants; Puberty, precocious; and under various endocrine glands
—— somatosexual aberrations in; role of adrenal cortex, 674†
—— urate metabolism in, 749*, 666†
—— urinary excretion of 17-ketosteroids in, 426*
—— young fraternal dissimilar twins; hyperthyroidism in, 298
CHLORIDE: *see also* Addison's disease; Electrolytes; Sodium; and under various endocrine glands
—— and sodium excretion; relative independence of, 368*
—— CO_2/Cl ratio of plasma in essential hypertension, 677†
—— in serum; increased in diabetic ketoacidosis, 1245*
CHLORIDE (cont.)
—— in serum; low, in hypokalemia, 691*
—— metabolism following ACTH intravenously, in man, 593*
—— metabolism following single dose of DOCA, 660†
—— nonchloruretic, antidiuretic substance extracted from urine, 652†
—— renal excretion of, in Cushing's syndrome, 13*
CHLORINE, replacing iodine in thyroxine; effect, 1099*, 1107*
CHOLESTEROL
—— effect of propylthiouracil and of feeding cholesterol on serum cholesterol and arterial intima of rat, 106
—— esterified; the immediate precursor of adrenal cortical steroids; effect of ACTH on serum cholesterol fractions, 656†
—— in blood: *see* Blood, cholesterol
—— in the dilution of DOCA pellets, 677†
—— with insulin: effect on absorption, 818*
CHORIONIC GONADOTROPIN: *see* Gonadotropins; Pregnancy, diagnosis
CHROMOPHOBE ADENOMA: *see* Pituitary, disorders
CIBA AWARD: *see* Association, awards
CINNAMIC ACID, phenyl-diiodohydroxy-; in study of organic *vs.* inorganic iodine, 1080*
CIRCULATION: *see* Blood; and Vascular system
CITRIC ACID
—— citric acid response to oral glucose; abnormalities in diabetes, 400
—— sodium citrate in treatment of hypercalcemic syndrome, 11*
CLIMACTERIC: *see also* Estrogens; Menstruation; Ovary
—— buccal tablets of estrogen in therapy of, 382*
—— changes in amounts of LH and FSH in urine of; effects of estrogen on, 668†
—— effect of estrogenic therapy on urethral smear in, 1362*
—— effect of synthetic Vitamin E in, 89*
—— effects of various estrogens on vaginal mucosa in, 480
—— postmenopausal woman; masculinizing ovarian tumor in, 774*
—— relation to tophaceous and pretophaceous gout, 749*
—— vaginal smears in; used in the assay of estrogens, 725*
COARCTATION OF AORTA: *see* Vascular system
COLD
—— hormonal alterations in men exposed

COLD (cont.)
to; effect of ACTH on, 529*
COLORIMETRIC METHODS: *see* Methods
COMMITTEES of the Association: *see* Association
COMPOUND E: *see* Adrenals, preparations and compounds
COMPOUND F: see Adrenals, preparations and compounds
CONFESSIONS of an elderly thyroidologist (belated 1948 presidential address of American Goiter Association), 974*
CONGENITAL ANOMALIES: *see also* under various endocrine glands
—— coarctation of aorta associated with abnormal digits, hypo-ovarianism and dwarfism, 622*
—— malformations, associated with rudimentary testes and dwarfism, 1333*
—— malformations of the kidney, with renal dwarfism, 401
CONVULSIONS, electrically induced in mental disease
—— changes in urinary uric acid-creatinine ratio after, 548*
—— decrease in eosinophiles after, 440*
CORPUS LUTEUM: *see* Ovary; Progesterone
CORTICOIDS; CORTICOSTEROIDS; CORTIN; CORTATE: *see* Adrenals, preparations and compounds; Steroids
COUNCIL of the Association: *see* Association
COURSES
—— in endocrinology, postgraduate; *see* Association, postgraduate assemblies; and University of California
—— in medical illustration, *see* University of Georgia
CRANIOPHARYNGIOMA: *see* Pituitary, disorders
CREATININE: *see also* Nitrogen; Protein; and under various endocrine glands
—— uric acid ratio, urinary:
— following ACTH intravenously, 593*
— following shock therapy, 548*
— in men exposed to heat and cold, 529*
CRETINISM: *see* Thyroid, disorders, hypothyroidism
CRYPTORCHISM: *see* Testis
CUBITUS VALGUS, associated with rudimentary testes and dwarfism, 1333*
CUSHING'S SYNDROME: *see also* Adrenal, disorders; Pituitary, disorders
—— adrenal tumor *vs.* hyperplasia; comparison of urinary 17-ketosteroids in, 680†
—— and severe diabetes mellitus; isolation of 17-hydroxycorticosterone from urine in, 478
CUSHING'S SYNDROME (cont.)
—— changes in urinary steroids in, produced by sodium deprivation and by DOCA, 661†
—— hypokalemic alkalosis in; effect of therapy, 663†
—— mechanism of action of testosterone in, 663†
—— plasma urate in; effect of removal of tumor, 749*
—— protein metabolic abnormality in, studied by S^{35}-labeled-methionine, 662†
—— renal excretion of salt and water in, 13*
—— "steroid diabetes" in; compound F in urine; N, P and Ca balances; necropsy, 672†
—— urinary prolactin in, 653†

DEBILITATING DISEASE
—— chronically ill and undernourished patients; potassium in, 691*
—— insulin content of pancreas reduced in, 481*
DELPHIAN lymph node: in Hashimoto's thyroiditis, and as an early sign of thyroid cancer, 1012*
DESOXYCORTICOSTERONE: *see* Adrenals, preparations and compounds
DEXTROSE: *see* Blood, sugar; Carbohydrate metabolism; Diabetes mellitus
DIABETES INSIPIDUS: *see* Pituitary, disorders
DIABETES MELLITUS: *see also* Blood, sugar; Carbohydrate metabolism; Insulin; Pancreas
—— abnormalities in citric acid response to oral glucose in, 400
—— acidosis; potassium deficiency associated with, 397
—— acidosis; potassium in the treatment of, 691*
—— acidosis; urinary excretion of corticosteroids in, 672†
—— alloxan diabetes in rabbits; retarded absorption of PZI pellets in, 818*
—— blood pressure and obesity in, 48*
—— blood sugar: *see* Blood, sugar
—— deaths from, in the District of Columbia during 42 years, 396
—— dextrose tolerance test: *see* Blood, sugar
—— electrolyte balance, in controlled and uncontrolled ketosis and acidosis in, 1259*
—— generalized allergy to insulin in, 895*
—— glucose tolerance test: *see* Blood, sugar
—— hypopotassemia during treatment of ketosis with insulin, 1245*

DIABETES MELLITUS (cont.)
—— in a Scottish diabetic clinic; etiology, hereditary factors, death rate, 48*
—— in infants under one year of age, 396
—— keto-acidosis; behavior of electrolytes during treatment, 673†
—— management of; present day methods, 395
—— metabolism of glucose and galactose in, 670†
—— more light on the biochemistry of, 1238*
—— sugar tolerance test: *see* Blood, sugar
—— urinary excretion of insulin in, 395
—— urinary 17-ketosteroid excretion in, 426*
COMPLICATIONS AND SEQUELAE
—— and acromegaly, 126*
—— and Addison's disease (autopsies), 245*, 403*
—— degenerative vascular lesions in, 394
—— development of, in Addison's disease (autopsy), 36*
—— family history of, in osteitis deformans, 385*
—— in a Scottish diabetic clinic, 48*
—— in pregnancy, 395
—— "steroid diabetes" with Cushing's syndrome; Na, P and Ca balances; necropsy, 672†
—— with thyrotoxicosis; blood ketones and other products of fat and protein catabolism in; effect of testosterone on, 671†
DIBROMESTRONE: *see* Estrogens
DIENESTROL: *see* Estrogens
DIET: *see also* Anorexia nervosa; Fat; Nutrition; Obesity; Vitamins
—— dietary factors (thiooxazolidone) in pathogenesis of simple goiter, 1069*
—— in the prolonged medical treatment of obesity, 275*
—— protein of; effect on ability of liver to inactivate estradiol in the rat, 675†
DIETHYLSTILBESTROL: *see* Estrogens
DIGITS: *see* Bones
DIHYDROTACHYSTEROL, in treatment of pseudohypoparathyroidism, 862*
DIIODOTHYRONINE: *see* Thyronine
DIODOTYROSINE, radioactive; used in study of mutual interconversion of organic and inorganic iodine, 1080*
DWARFISM: *see also* Growth; Pituitary
—— associated with coarctation of aorta, abnormal digits, and ovarian insufficiency, 622*
—— associated with rudimentary testes and congenital malformations, 1333*
—— pituitary; treated with growth and thyrotropic hormones, 655†
DWARFISM (cont.)
—— renal; with hyperparathyroidism and congenital malformation of the kidneys, 401
—— with Addison's disease and diabetes mellitus, 403*
DYSGERMINOMA: *see* Ovary, tumors

ECLAMPSIA: *see* Pregnancy
EDEMA
—— localized, solid; in association with exophthalmic goiter, 883*
—— of pregnancy; cortical steroid excretion in, 319*
EDITOR, LETTERS TO: *see* Association, letters to the editor
EDITORIAL BOARD and Editor of the Journal: *see* Association
ELECTROCARDIOGRAM: *see* Heart
ELECTROCONVULSIVE THERAPY: *see* Convulsions
ELECTROENCEPHALOGRAM: *see* Brain
ELECTROLYTES: *see also* under specific chemical element involved; and under various endocrine glands
—— during treatment of diabetic keto-acidosis, 673†
—— effect of ACTH intravenously on, in man, 593*
—— effect of Compound E on, in Addison's disease, 660†
—— effect of single dose of desoxycorticosterone acetate on, in normal man, 660†
—— following single injection of ACTH, 661†
—— in controlled and uncontrolled diabetic ketosis and acidosis, 1259*
—— in Cushing's syndrome with "steroid diabetes," 672†
—— in hypokalemia, 691*
—— in pregnancy with Addison's disease, 514*
—— in serum, in Addison's disease, 1324*
—— in serum, in Cushing's syndrome; effect of KCl and testosterone therapy, 663†
—— in serum; in tumors at or near the pituitary, 1292*
—— relative independence of sodium and chloride excretion, 368*
EMOTIONAL STRESS: *see also* Stress
—— role of, in survival of treated adrenalectomized rats, 678†
EMPHYSEMA, mediastinal, and pneumothorax, following thyroidectomy, 987*
ENCEPHALOGRAM: *see* Brain
ENDOCRINE: *see also* Androgens; Estrogens; Gonadotropins; Hormones; Steroids; and under various glands

ENDOCRINE (cont.)
—— disorders; incidence of cancer in, 682†
—— disorders, various; relative independence of sodium and chloride excretion in, 368*
—— literature, abstracts of: *see* Abstracts
—— reviews, 171*, 557*
ENDOMETRIUM; ENDOMETRIOSIS: *see* Uterus
ENERGY metabolism: *see* Basal metabolism; Exercise; Temperature
ENZYMES: *see also* Blood
—— amino acid oxidase; effect of vitamin B, thyroid, and adrenalectomy on, in the rat, 684†
—— pepsidases in serum; effect of ACTH intravenously in man, 593*
—— phenosulphatase; in analysis of human pregnancy urine for conjugated sulphates of estrogens, 667†
—— phosphatase, alkaline, in serum; relation to carbohydrate metabolism in dogs, 907*
—— proteolytic; in the study of the thyroid gland, 298
EOSINOPHILES: *see* Blood, cells
EPINEPHRINE: *see* Adrenals, preparations, epinephrine
EPIPHYSES: *see* Bones
EPITHELIUM: *see* organ involved
EQUINE gonadotropin: *see* Gonadotropins
ERRATUM, 113
ESSAYS winning Van Meter Prize Award and honorable mentions, *see* American Goiter Association
ESTERS of testosterone, new; androgenic activity compared with testosterone propionate, 679†
ESTRADIOL; ESTRIOL; ESTRONE: *see* Estrogens
ESTROGENS: *see* also Climacteric; Gonadotropins; Hermaphrodism; Hormones; Menstruation; Ovary; Pregnancy; Progesterone; Puberty, precocious; Steroids
—— analysis of feminizing testicular tumor for, 579*
—— assay of theca-cell tumors of ovary for, 111
—— estrogen-producing Sertoli cell tumors of human testis and ovary, 301*
—— interrelation with vitamins, 557*
—— production by the testis, 579*
—— role in development of axillary and pubic hair, 555*
—— urate metabolism; sex difference in, 749*
EFFECTS AND THERAPY
—— activity of; limitations of vaginal smear glycogen as an index of, 1359*
ESTROGENS (cont.)
EFFECTS AND THERAPY (cont.)
—— assayed by means of human vaginal smear, 725*
—— buccal administration of, in tablets, 382*
—— effect on excretion of total and luteinizing gonadotropins in castrate female, 636*
—— effect on excretion of urinary gonadotropin in eunuchoid men, 113*
—— effect on urate metabolism in pseudohermaphrodism, 749*
—— effect on urinary gonadotropin in castrated female, 654†
—— estradiol benzoate (pellets) and other estrogens; effect on urethral and urinary sediment smears in the female, 1362*
—— estradiol esters more effective than stilbene derivatives in releasing luteinizing hormone in menopausal women, 668†
—— ethinyl estradiol; comparison of oral and intramuscular routes of administration, 573*
—— gynecomastia: *see* Breasts, gynecomastia
—— hyperestrinism induced by large doses of stilbestrol dipropionate; glycopenic vaginal smear in, 1359*
—— in acromegaly, 126*
—— in hyperthroidism, 330*
—— in staphylococcus infections, 680†
—— influence on rate of radioiodide uptake, 430*
—— intravenously, in gynecic disorders, 681†
—— intravenously injected sex and other hormones; effect on blood flow in human endometrium, 111
—— "priming" with, necessary for full effect of progesterone therapy, 736*
—— reproduction of menstrual changes by, in cervical mucus of human castrates, 479
—— stilbestrol; large doses of, in management of threatened abortion, 669†
—— toxemia (hypercalcemic syndrome) from, in patients with osteolytic metastases, 1*
—— use of, in medicine, 480
—— various; comparison of effects on vaginal mucosa, 480
—— various; comparison of potencies, and of routes of administration, 725*
METABOLISM
—— a review, 557*

ESTROGENS (cont.)
METABOLISM (cont.)
—— conjugated sulphates of, in human pregnancy urine, 667†
—— dibromestrone; tissue localization and excretion route of, 112
—— effect of progesterone on metabolism of, 557*
—— inactivation of, by liver; effect of dietary protein on, in rat, 675†
—— inactivation of, in women with vitamin B deficiency, 402
—— urinary; comparison of methods for hydrolysis of conjugated estrogens, 480
—— urinary; in acromegaly and granulosa cell tumor of ovary, 630*
—— urinary; in male dog with feminizing testicular tumor, 579*
—— urinary; in pregnant woman with Addison's disease, 514*
—— urinary; in pseudocyesis, 668†
—— urinary; in testicular chorioma: effect of removal of tumor, 615*
ESTRONE: *see* Estrogens
ESTRUS cycle in normal rat; excretion of 17-ketosteroids in, 795*
ETHINYL ESTRADIOL: *see* Estrogens
EUNUCHISM AND EUNUCHOIDISM: *see* Testis, disorders; Androgens; Pituitary
EXERCISE
—— effect on leukocytes and eosinophiles, 714*
—— eosinophiles and adrenal cortical activity in men, during, 529*
EXOPHTHALMIC GOITER: *see* Thyroid, disorders, hyperthyroidism
EXOPHTHALMOS: *see* Eyes; and Thyroid, disorders
EYES
—— changes in acromegaly, 126*
—— exophthalmos; effect of radioiodine therapy on, 29*
—— exophthalmos; effect of various doses and iodination of pituitary extract on; effect of ACTH and of DOCA on production of, in guinea pigs, 913*, 927*, 937*
—— exophthalmos, malignant; studied by radioiodine, 342*
—— exophthalmos; parallelism with myxedema circumscription thyrotoxicum, 883*
—— exophthalmos; relation to type of parenchymal replacement in hyperplastic thyroid gland, 1202*
—— visual fields in case of pituitary tumor; effect of androgen therapy, 372*

FAMILIAL
—— factor, in cancer and in endocrine disease, 682†
—— family history, in diabetes mellitus, 48*
—— family history, in gout, 749*
—— family history of diabetes in osteitis deformans, 385*
FAT: *see also* Cholesterol; Diabetes mellitus, ketosis; Lipids; Nutrition; Obesity
—— lipid content of certain ovarian and testicular tumors, 301*, 579*, 774*
—— metabolism; effect of steroid hormones on blood ketones and other products of fat catabolism, 671†
—— mobilization of; effect of various doses and iodination of pituitary extract; effect of ACTH and of DOCA on, in guinea pigs, 913*, 927*, 937*
—— mobilization of, to the liver; influence of adrenal cortex and thyroid, in the mouse, 657†
FELLOWSHIPS: *see* Awards
FERTILITY: *see* Sterility
FETUS: *see also* Infants; Pregnancy
—— death of; hormonal test for, 402
—— effect on, of thiouracil in treatment of mother for thyrotoxicosis, 903*
—— function of adrenal cortex in, 646*
FIBROSIS: *see* Tissues; and under specific organs
FLUOROTHYRONINE: *see* Thyronine
FOLIC ACID: *see* Vitamins
FOLLICLE-STIMULATING HORMONE (FSH): *see* Gonadotropins; Pituitary
FRIEDMAN TEST: *see* Pregnancy; Tests
FROGS
—— care and maintenance of, for pregnancy test, 1372*
—— male; hormonal factors producing sperm release in, 668†
FROHLICH'S SYNDROME: *see* associated with Ovarian, Pituitary and Testicular disorders
FSH: *see* Gonadotropins; Pituitary

GALACTOSE: *see* Carbohydrate metabolism
GAMMA RAY counting, in measurement of urinary I^{131}, 841*
GASTRO-INTESTINAL TRACT
—— concentration of radioactivity in, in study of labeled iodocasein in myxedema, 828*
—— enterogastrone; effect on histamine and insulin stimulated gastric secretion in man, 399
—— gastric hyperacidity following insulin shock therapy, 394
—— radioactive iodine in feces after oral

GASTRO-INTESTINAL TRACT (cont.)
and i.v. administration of labeled racemic thyroxine in myxedema, 1406*
——radioactive iodine in feces following administration of labeled iodide, thyroglobulin and thyroxine in myxedema, 1392*
GLUCOSE: *see* Blood, sugar; Carbohydrate metabolism; Diabetes mellitus; Insulin
GLYCINE, *see* Carbohydrate metabolism
GLYCOGEN: *see also* Carbohydrate metabolism; Diabetes mellitus; Liver
——in muscle; influence of DOCA on, in Vitro, 397
—— in vaginal smear; limitations of, as an index of estrogen activity, 1359*
GLYCOSURIA: *see* Carbohydrate metabolism; Diabetes mellitus
GOITER: *see* Thyroid, disorders
GOITROGENS: *see also* Thiouracil; and Thyroid disorders
—— a naturally occurring goitrogen, thiooxazolidone, 1069*
—— effect on fetus, 903*
—— in hyperthyroidism, 1232*
—— in thyrotoxicosis complicating pregnancy, 903*
—— study of thyroxine, tetrabrom- and tetrachlorthyronine, 1099*, 1107*
GONADOTROPINS: *see also* Pituitary, preparations; Pregnancy
—— antigonadotropin formation in man, 654†
—— antigonadotropins complicating treatment of infertile men, 213*
—— antihormones to; effect on sperm, testis and urinary gonadotropins, 355*
—— chorionic, and testosterone; spermatogenesis following therapy with, 1245*
—— chorionic; antihormone formation during therapy with, 384*
—— chorionic; effect of various methods of administration on excretion of, 268*
—— chorionic; local systemic reaction to injection of beeswax solution, 268*
—— chorionic; spermatogenesis following administration of; coincidental neoplasm, 163*
—— effect on sperm release in frog, used as test for pregnancy, 668†
—— equine; for intravenous use in gynecic disorders, 681†
—— evaluation and differentiation of, by their action on the male toad, 297
—— in pregnancy: *see* Pregnancy, tests
IN URINE
—— chorionic: *see* also Pregnancy, tests
—— chorionic; in cases of blighted ovum, 676†
GONADOTROPINS (cont.)
IN URINE (cont.)
—— chorionic; in hyperthyroidism, 330*
—— chorionic, in pregnant and nonpregnant women; following various methods of administration, 268*
—— chorionic in serum and urine; in pregnancy, in neoplasm of testis and in hydatidiform mole, 615*
—— effect of antihormones on, 355*
—— effect of pituitary antihormone on, in infertile men, 355*
—— estimation of total and luteinizing gonadotropins in, in males and nonpregnant females, 654†
—— Friedman test in masculinizing tumor of ovary, 774*
—— FSH and LH in urine of menopausal women; action of estrogens on release of LH, 668†
—— FSH in paraplegic males with gynecomastia, 457*
—— in adrenal cortical carcinoma in a male, 451*
—— in eunuchoid men; inability of testosterone to reduce, 113*
—— in feminizing testicular tumor in male dog, 579*
—— in infertile men, 213*
—— in male hypogonadism, 1245*
—— in precocious puberty associated with ovarian dysgerminoma, 1349*
—— in pregnancy: *see* Pregnancy, tests
—— in pregnant woman with Addison's disease, 514*
—— in pseudocyesis, 668†
—— in test for fetal death, 402
—— in Turner's syndrome in a male, 1333*
—— in uterine leiomyoma; effect of progesterone therapy, 1273*
—— method for differentiation of, in nonpregnant females and in males, 636*
GONADS: *see* Androgens; Estrogens; Gonadotropins; Hermaphrodism; Ovary; Testis
GOUT
—— characteristic urinary 17-ketosteroid and androgen findings in, 497*
—— marked difference between tophaceous and pretophaceous in women, 749*
—— sex, and age difference in urate metabolism in, 749*, 666†
GRANTS: *see* Awards
GRAVES' DISEASE: *see* Thyroid, disorders, hyperthyroidism
GROWTH: *see also* Children; Dwarfism; Ovary; Pituitary; Puberty, precocious; Testis

GROWTH (cont.)
—— hormone, *see also* Pituitary, preparations
—— hormone of pituitary in treatment of pituitary dwarfism, 655†
—— physical, during adolescence, 400
GUTERMAN TEST: *see also* Pregnancy, tests
—— modification of, 852*
GYNECOMASTIA: *see* Breast

HAIR: *see also* Cushing's syndrome; Hermaphrodism; Puberty, precocious; Virilism; and under various endocrine disorders
—— axillary; growth of, as an index of endocrine status; relation to urinary steroids, 665†
—— axillary, in the male; local action of testosterone on development of, 1434*
—— axillary and pubic; loss of, in woman with Addison's disease and regular menstruation, 555*
HIRSUTISM
—— associated with Leydig-cell ovarian tumor, 486*
—— associated with masculinizing ovarian tumor, 774*
—— idiopathic; excretion of 17-ketosteroids, in, 795*
—— in areas of myxedema circumscription thyrotoxicum, 853*
HEART
—— angina pectoris; treatment with propylthiouracil, 106
—— auricular fibrillation; relation to type of parenchymal replacement in hyperplastic thyroid gland, 1202*
—— effect of potassium on human electrocardiogram, 691*
HEAT
—— hormonal alterations in men exposed to; effect of ACTH on, 529*
—— production, *see* Basal metabolism; Exercise; Temperature
HEIGHT: *see* Children; Dwarfism; Growth
HERMAPHRODISM: *see also* Ovary; Puberty, precocious; Testis; Virilism
—— and pseudohermaphrodism in children; adrenal cortical function in, 674†
—— pseudohermaphrodism with adrenogenital syndrome; urate metabolism in; effect of stilbestrol and of surgery, 749*
HIRSUTISM: *see* Hair
HONORABLE MENTIONS, for Van Meter Prize; *see* American Goiter Association
HORMONES: *see also* Androgens; Estrogens; Gonadotropins; Insulin; Progesterone; Steroids; and under various endocrine glands
—— antihormones, *see* Antihormones
—— hormonal alterations in men exposed to heat and cold stress; effect of ACTH on, 529*
—— incidence of cancer in endocrine case histories, 682†
HÜRTHLE CELLS: *see* Thyroid, disorders and pathology
HYDATIDIFORM MOLE: *see* Uterus
HYPERCALCEMIA AND HYPERCALCEMIC SYNDROME: *see* Blood, calcium; Calcium metabolism; Kidney; Parathyroids
HYPEREMIA TEST: *see* Ovary; Pregnancy, tests; Tests
HYPERGLYCEMIA: *see* Blood, sugar; Carbohydrate metabolism; Diabetes mellitus
HYPERMETABOLISM: *see also* Basal metabolism
—— associated with pheochromocytoma, 782*
—— studied under pentothal anesthesia, 1190*
HYPERSENSITIVITY: *see* Allergy; and under preparation involved
HYPERTENSION: *see* Vascular system
HYPERTHYROIDISM: *see* Thyroid, disorders, hyperthyroidism
HYPERTRICHOSIS: *see* Hair, hirsutism
HYPERURICEMIA, idiopathic; urinary 17-ketosteroids in, 497*
HYPERVENTILATION; effect on blood pressure in pheochromocytoma, 782*
HYPOGENITALISM: *see* Hermaphrodism; Menstruation; Ovary, disorders; Pituitary, disorders; Sterility; Testis, disorders
HYPOGLYCEMIA: *see* Blood, sugar; Carbohydrate metabolism; Diabetes mellitus; Insulin
HYPOGONADISM: *see* Hermaphrodism; Menstruation; Ovary, disorders; Pituitary, disorders; Sterility; Testis, disorders
HYPOKALEMIA, 691*
HYPOTHALAMUS
—— hypothalamic manifestations with pheochromocytoma, 782*
—— tumors near the pituitary; SPI in, 1292*
HYPOTHYROIDISM: *see* Thyroid, disorders, hypothyroidism

IMPLANTATION: *see* Administration; and under Adrenal preparations; Androgens; Estrogens; Insulin; Progesterone

IMPOTENCE: *see* Sterility; Testis
INDEX, to Volume 9 (1949)
—— author, 1443
—— subject, 1455
INFANT: *see also* Congenital anomalies; Children; Fetus; Pregnancy
—— diabetes mellitus in, 396
—— excretion of neutral lipid-soluble reducing substances in, as index of adrenal cortical function, 646*
—— followed for sixteen months; mother treated with thiouracil for thyrotoxicosis when pregnant, 903*
—— somatosexual aberrations in; role of adrenal cortex, 674†
—— with pseudohypoparathyroidism, 862*
INFANTILISM: *see* Dwarfism; Growth; Ovary; Pituitary; Testis
INFECTIONS
—— associated with onset of diabetes; incidence, 48*
—— staphylococcus; sex hormone therapy of, 680†
INFERTILITY: *see* Sterility
INFLAMMATION: *see* Infections
INSULIN: *see also* Blood, sugar; Carbohydrate metabolism; Diabetes mellitus; Pancreas
—— and histamine-stimulated gastric secretion; influence of enterogastrone on, 399
—— content of pancreas reduced in nondiabetics dying of debilitating disease, 471*
—— effect on adrenal activity in diabetes, 672†
—— effect on adrenal cortical hormone in blood of dogs, 658†
—— effect on electrolyte balance, particularly of potassium, in diabetes mellitus, 1245*
—— for relief of pain in osteitis deformans, 385*
—— generalized allergy to, 895*
—— human; preparation of, for experimental use, 481*
—— hyperglycemic effect of, 398
—— hypoglycemia from small doses of; prevention by hyperglycemic factor extracted from pancreas, 669†
—— hypoglycemia in the rat; stimulation of nitrogen metabolism by adrenal cortical extract during, 657†
—— in treatment of diabetes mellitus with Addison's disease, 403*
—— protamine-zinc; for successful implantation in normal and diabetic rabbits, 818*
—— requirements in case of Addison's disease combined with diabetes mellitus, 245*
—— sensitivity in decerebrate rats, 670†
—— shock therapy; gastric hyperacidity following, 394
—— studies in biochemistry of, with aid of radioactive carbon, 1238*
—— tolerance curve in Turner's syndrome in a male, 1333*
—— tolerance, in masculinizing tumor of ovary, 774*
—— unusual sensitivity to, in diabetes mellitus following Addison's disease, 36*
—— urinary excretion of, by normal and diabetic subjects, 395
IODINE: *see also* Thiouracil; Thyroid
—— and goiter in Yunnan province, 684†
—— effect of iodide ion on thyroid iodine utilization, in euthyroidism and in hyperthyroidism, 941*
—— *in blood, see* Blood, iodine
—— iodide clearance of thyroid, in normal subjects, 941*
—— iodinated thiouracils; antithyroid action of, 801*
—— iodination of pituitary extract; effect on thyrotropic, exophthalmic and fat-mobilizing principles of, 927*
—— mechanism of release of iodized compounds from the thyroid, 149*
—— organic and inorganic; their reciprocal metabolic fates; hormonal *vs.* nonthyroid iodine, 1080*
—— stable; effect of, on radioiodine uptake of thyroid, 342*
—— strong solution of, in treatment of hyperthyroidism, 1232*
—— therapy, in pheochromocytoma with excessive hypermetabolism, 782*
—— urinary excretion of I^{127} in estimation of rate of thyroid hormone formation in man, 941*
RADIOACTIVE
—— diiodotyrosine and derivatives, in study of "thyrenzyme," 1080*
—— distribution in tissues after injection into rats, 1080*
—— distribution of, in a patient with metastatic adenocarcinoma of the thyroid (necropsy), 1379*
—— fecal and urinary excretion and blood levels in myxedema, following administration of labeled iodide, thyroglobulin and thyroxine, 1392*
—— fecal and urinary excretion, blood levels, and in vivo observations, in study of labeled iodocasein in myxedema, 828*

IODINE (cont.)
RADIOACTIVE (cont.)
—— in blood, urine and tissues in myxedema, following labeled and unlabeled racemic thyroxine, orally and i.v., 1406*
—— in estimation of rate of thyroid hormone formation in man; thyroid uptake and urinary excretion of I^{131}, 941*
—— in expired air (pulmonary clearance), in serum and in urine, in thyroid carcinoma, 1080*
—— in study and treatment of thyroid disease; a review, 171*
—— in study of antithyroid activity of foods, 1069*
—— in study of functional capacity of malignant thyroid tumors, 1012*, 1153*, 1171*
—— in study of iodinated thiouracils, 801*
—— in study of thyroid function in man, 342*
—— in treatment of hyperthyroidism, 29*, 1232*, 298, 300
—— in treatment of metastases from cancer of thyroid, 1122*, 1138*
—— labeled sodium iodide compared with labeled iodocasein, in myxedema; metabolism of, 828*
—— labeled thyroglobulin and thyroxine; behavior of, in myxedema, 1392*
—— radioautography in preoperative estimation of function in thyroid nodules, 1171*
—— radioautography in study of iodine uptake in normal and malignant tissues, 1379*
—— six-year follow-up of metastatic thyroid cancer patient, treated with, 1122*
—— thyroid collection of, and PBI, in senescence, hypothyroidism and hypopituitarism, 430*
—— thyroid uptake of; effect of adrenal compounds on, in Addison's disease and in panhypopituitarism, 659†, 660†
—— thyroid uptake of, in various endocrinopathies, 342*
—— toxic effects from therapy with, 1138*
—— tracer technique with I^{131} as substitute for BMR, 664†
—— urinary; comparison of measurements by beta and by gamma ray counting, 841*
—— urinary excretion of, as aid in diagnosis of hyperthyroidism, 299
IODINE (cont.)
RADIOACTIVE (cont.)
—— urinary excretion of, in metastatic thyroid cancer; effect of TSH and of thiouracil on, 1138*
—— urinary excretion of, in normal subjects and in myxedema, 171*
—— urinary excretion of, in thiocyanate goiter with myxedema, 446*
—— used to visualize mechanism of secretion of thyroid hormone, 149*
—— utilization of, by thyroid cancer metastases to bone; studied by radioautography, 1122*, 1138*
IODOCASEIN, labeled; behavior in human myxedema, 828*
IRRADIATION: *see* Radioactive; and Roentgen ray

JEFFERSON Medical College and Hospital Fellowship, 212, 292

KELLOGG FOUNDATION, fellowships for Latin-American Physicians, 689
KETONES: *see* Blood; Diabetes mellitus
KETOSIS: *see* Diabetes mellitus
KETOSTEROIDS AND 17-KETOSTEROIDS: *see* Steroids
KIDNEY: *see also* Urine
—— antidiuretic, nonchloruretic substance extracted from urine, 652†
—— effect on distribution and metabolism of circulating testosterone, 665†
—— function in adrenal insufficiency, 109
—— function, in gout, 497*
—— in Addison's disease combined with diabetes mellitus (autopsy), 245*
—— in Cushing's syndrome, 13*
—— nephrosclerosis associated with pheochromocytoma, 782*
—— nephrosclerosis; relation to alarm reaction, 479
—— nephrotic syndrome; plasma urate in; effect of ACTH on, 749*
—— possible role in separating hormones and antihormones, 213*
—— renal clearance in cirrhosis of the liver, 682†
—— renal clearance of chorionic gonadotropin in pregnancy, neoplasm of testis, and hydatidiform male, 615*
—— renal dwarfism with hyperparathyroidism and congenital malformation of the kidneys, 401
—— renal function in normal and adrenalectomized rats following saline or adrenal steroid administration, 658†
—— renal insufficiency and nephrocalcinosis associated with sex hormone therapy for osteolytic metastases, 1*

KIDNEY (cont.)
—— role of, in the potassium deficiency of alkalosis, 676†
—— urate clearance and glomerular filtration rate, in gout, 749*

LABOR: *see* Pregnancy; Uterus
LACTATION: *see* Breast; Pituitary, prolactin; Pregnancy
LATIN-AMERICAN PHYSICIANS: fellowships for, 689
LAURENTIAN HORMONE CONFERENCE FOR 1949
—— announcements of, 393, 577
—— program of, 577
LEIOMYOMA: *see* Uterus
LETTERS TO THE EDITOR: *see* Association, letters to the editor
LEUKEMIA
—— lymphatic; width of adrenal cortex in 158*
LEUKOCYTES: *see* Blood, cells
LEYDIG CELL: *see also* Testis
—— tumor of ovary, with virilism, 486*
LIPIDS: *see also* Cholesterol; Fat
—— abundant, in feminizing testicular tumor, 579*
—— in serum, *see* Blood
—— in urine and serum, in pituitary disease, 1292*
—— lipoid content of estrogen-producing Sertoli cell tumors, 301*
—— lipoid content of masculinizing ovarian tumor, 774*
LITERATURE, current endocrine; abstracts of; *see* Abstracts
LIVER
—— bile; high concentration of dibromestrone in, after injection, 112
—— cirrhosis of; renal clearance in, 682†
—— cirrhotic patients; antidiuretic nonchloruretic substance extracted from urine of, 652†
—— concentration of radioactivity in, in study of labeled iodocasein in myxedema, 818*
—— effect on distribution and metabolism of circulating testosterone, 665†
—— fat deposition in: effect of various doses and iodination of pituitary extract; effect of ACTH and of DOCA on, in guinea pigs, 913*, 927*, 937*
—— function, in gout, 497*
—— hepatitis; metabolism of glucose and galactose in, 670†
—— hepatosplenomegaly associated with corticoadrenal tumor, goiter and gynecomastia, 255*
—— inactivation of estradiol by; effect of dietary protein on, in rat, 675†
LIVER (cont.)
—— mobilization of fat to; possible involvement of adrenal cortex and thyroid, in the mouse, 657†
—— radioactivity over, after administration of labeled thyroglobulin and thyroxine, in myxedema, 1392*
—— radioiodine in, fifty-six hours after ingestion of, for thyroid cancer, 1379*
—— role in inactivation of estrogens, 557*
—— "thyroxine space" in, studied by radiothyroxine in myxedema, 1406*
LUTEINIZING HORMONE: *see* Gonadotropins; and Pituitary, preparations
LYMPHOCYTES: *see* Blood, cells; and Lymphoid tissue
—— lymphocytic infiltration, in cellular involution of the thyroid, 874*
—— lymphocytic infiltrations in thyroid and liver, in Addison's disease and diabetes mellitus (autopsy), 36*
—— lymphocytic infiltration of ovarian dysgerminoma, 1349*
—— lymphocytic replacement in hyperplastic thyroid; statistical study of clinical significance, 1201*
—— lymphosarcoma, *see* Lymphosarcoma
—— struma lymphomatosa, Hashimoto's disease, *see* Thyroid, disorders
LYMPHOID TISSUE: *see also* Lymphocytes
—— diseases; width of adrenal cortex in, 158*
LYMPHOSARCOMA
—— of the thyroid, 1043*
—— width of adrenal cortex in, 158*

MALNUTRITION: *see* Anorexia nervosa; Nutrition; Vitamins
MANNITOL, renal excretion of, in Cushing's syndrome, 13*
MARE gonadotropin, *see* Gonadotropins, equine
MASTITIS: *see* Breast
MEDICAL ILLUSTRATION, course in, 295
MENOPAUSE: *see* Climacteric
MENSTRUATION: *see also* Climacteric; Estrogens; Pregnancy; Progesterone; Ovary; Puberty, precocious; Uterus; Vagina, smears
—— circulating eosinophiles during cycle, 714*
—— cyclic changes in cervical mucus produced artificially in human castrates, 479
—— disorders of; intravenous estrogen in, 681†
—— effect of alpha-tocopherol on pregnanediol excretion during cycle, in

MENSTRUATION (cont.)
normal and in sterile women, 743*
—— effect of progesterone therapy for uterine leiomyoma on, 1273*
—— functional menstrual disorders; antigonadotropin formation in, during treatment, 654†
—— gonadotropin excretion in, 636*
—— in eight-year-old girl with ovarian dysgerminoma, 1349*
—— *menopause*, *see* Climacteric
—— metrorrhagia, associated with tubular testicular adenoma of ovary, 301*
—— normal cycle and gynecic disorders; correlation of vaginal smear and endometrial biopsy in, 673†
—— ovulation, *see also* Ovary; Progesterone; Sterility
—— prediction of time of human ovulation, by rat ovarian hyperemia test, 110
—— pregnanediol in urine during normal cycle, 234*, 852*
—— regular, in spite of loss of axillary and pubic hair, in woman with Addison's disease, 555*
—— relation to ketosteroid excretion in normal women and in idiopathic hirsutism, 795*
—— serum protein-bound iodine during normal cycle, 768*
AMENORRHEA
—— diagnosis and classification of; progesterone withdrawal test in, 110
—— during androgen therapy for bone metastases from breast cancer, 1314*
—— effect of estrogen therapy on urethral smear in, 1362*
—— following radioiodine therapy for thyroid cancer, 1138*
—— of acromegaly, dispelled by granulosa cell tumor of ovary, 630*
—— secondary; comparison of routes of administration of progesterone in, 736*
MENTAL DISEASE: *see also* Brain; Nervous System; Psychoneurosis
—— decrease in eosinophiles following electroconvulsive therapy for, 440*
—— changes in urinary, uric acid-creatinine ratio, after shock therapy for, 548*
—— insulin shock therapy in; gastric hyperacidity following, 394
—— thyroid therapy in, 298
METABOLISM: *see* Basal metabolism; Hypermetabolism; and under specific substances concerned
METHIONINE, S^{35}-labeled, in the study of protein metabolism in Cushing's syndrome, 662†
METHODS: *see also* Administration; Pregnancy, tests; Tests
—— comparison of biologic and chemical methods for urinary corticoids, 659†
—— comparison of methods for hydrolysis of conjugated urinary estrogens, 480
—— for assay of prolactin in human urine, 653†
—— for care and maintenence of toads and frogs for pregnancy test, 1372*
—— for differentiation of urinary gonadotropins of nonpregnant humans, 636*
—— for direct estimation of rate of thyroid hormone formation in man; and for calculating serum iodide, 941*
—— for measuring intercorneal distance, in study of exophthalmos in animals, 913*
—— for obtaining urethral smear in the female, 1362*
—— for preparation of human insulin for experimental use, 481*
—— for radioautographic estimation of thyroid nodules, 1171*
—— measurement of urinary I^{131} by beta and by gamma ray counting; a comparison, 841*
—— modification of Guterman pregnanediol test for pregnancy, 852*
—— new colorimetric; for pregnanediol, 399
—— of administration, *see* Administration; and various substances involved
—— rapid colorimetric, for sodium in biologic fluids, 95*
—— simple; for estimation of blood sugar, 394, 397
—— simplified; for determination of protein-bound blood iodine, 1185*
—— simplified; for quantitative colorimetric estimation of pregnanediol in urine, 479
METHYLTESTOSTERONE, *see* Androgens
METHYLTHIOURACIL: *see* Thiouracil
MUSCLES: *see also* Creatinine; Nutrition; Potassium; Protein; Uterus
—— debilitating disease; effect on insulin content of pancreas, 471*
—— effect of potassium on, 691*, 1259*
—— exercise; effect on adrenal cortical activity and eosinophiles in men, 471*
—— exercise; effect on leukocytes and eosinophiles, 714*
—— leiomyomas, uterine; effect of progesterone on, 1273*
—— the myogram in normal subjects and in those with Addison's disease, thyrotoxicosis and progressive muscular atrophy, 401

MUSCLES (cont.)
—— utero-tubal persufflation curve, in myxedema, 285*
MYXEDEMA: *see* Thyroid, disorders, hypothyroidism

NATIONAL RESEARCH COUNCIL
—— Committee on Growth: recommendations for British American exchange fellowships of American Cancer Society, 575
—— grants for research in endocrinology (1949–50), 102
NECK, webbed, associated with rudimentary testes and dwarfism, 1333*
NEOPLASMS: *see* Tumors; and under various endocrine disorders
NEPHROSCLEROSIS; NEPHROSIS: *see* Kidney
NERVOUS SYSTEM: *see also* Brain; Emotion; Mental; Psychoneurosis
—— nervous instability *vs.* hyperthyroidism: differential diagnosis of: by antithyroid drugs, 1054*; by basal metabolism testing under pentothal anesthesia, 1190*
—— in hypokalemia, 691*, 1259*
—— sympathicotropic cell tumor of ovary, 486*
NEUTROPHILES: *see* Blood, cells
NITROGEN: *see also* Blood; Creatinine; Protein; Uric acid
—— balance in Cushing's syndrome with "steroid diabetes," 672†
—— balance in diabetes mellitus with Addison's disease, 403*
—— balance in diabetic keto-acidosis, treated with insulin, 1245*
—— metabolism, following single injection of ACTH, 661†
—— metabolism; stimulation of, by adrenal cortical extract, during insulin hypoglycemia in the rat, 657†
—— total amino acids and glycine in various pathologic conditions, 398
—— urinary, increased following ACTH intravenously, 593*
NOR-EPINEPHRINE, in adrenal medulla, 652†
NOTICES: *see* Announcements
NUTRITION: *see also* Anorexia Nervosa; Diet; Obesity; Vitamins
—— chronic malnutrition in the rat; adequacy of ACTH function in, 656†
—— debilitating disease; effect on insulin content of pancreas, 471*
—— effect of fasting on diabetes mellitus following Addison's disease, 36*
—— potassium; in chronically ill, undernourished patients, 691*

OBESITY: *see also* Fat; Nutrition; and associated with endocrine disorders
—— effect of large single dose of thyroid globulin in, 377*
—— hemosedimentation test in, 683†
—— in diabetes mellitus, 48*
—— radioiodine uptake of thyroid in, 342*
—— results of prolonged medical treatment with diet—alone, with thyroid, and with amphetamine, 275*
OFFICERS of the Association: *see* Association, officers
OLIGOSPERMIA: *see* Testis, disorders, spermatozoa
ORAL, methods of administration; comparison with other methods, *see* Administration
—— buccal tablets of estrogen in treatment of ovarian deficiency, 382*
—— intraoral DCA tablets in treatment of Addison's disease, 1324*
OSTEITIS: *see* Bones
OVARY: *see also* Breast; Climacteric; Estrogens; Gonadotropins; Hermaphrodism; Menstruation; Pregnancy; Progesterone; Puberty, precocious; Sex; Sterility; Uterus; Vagina; Virilism
DISORDERS
—— amenorrhea, *see* Menstruation
—— blighted ovum; pregnanediol excretion in patients with, 676†
—— castrated females; differentiation of urinary gonadotropins in, 636*
—— climacteric, *see* Climacteric
—— deficiency; treated with buccal tablets of estrogen, 382*
—— failure; excretion of total and luteinizing gonadotropins in, 636*
—— insufficiency, associated with coarctation of the aorta, dwarfism, 622*
—— menopause, *see* Climacteric
—— menstrual disorders, *see* Menstruation
—— precocious puberty, *see* Puberty precocious
—— pseudohermaphrodism, *see* Hermaphrodism
—— *therapy: see* Estrogens; Gonadotropin; Progesterone
Tumors
—— dysgerminoma, in 8-year-old girl; the only case of precocious puberty with hormone assays, 1349*
—— estrogen-producing Sertoli cell tumors of, (androblastoma tubulare lipoides), 301*
—— granulosa cell tumor and acromegaly, 630*

OVARY (cont.)
DISORDERS (cont.)
Tumors (cont.)
—— masculinizing, in a postmenopausal woman, 774*
—— sympathicotropic (Leydig) cell tumor of, with virilism, 486*
—— theca-cell; 15 cases and review of literature, 111
—— virilizing, 112
PHYSIOLOGY
—— hyperemia of, in mouse, as a method for estimating urinary luteinizing gonadotropins in nonpregnant human, 636*, 654†
—— hyperemia of, in rat, used in 2-hour pregnancy test, 479
—— lack of uptake of iodine by, following treatment with radioiodine, 1138*
—— normal nonpregnant women; differentiation of urinary gonadotropins in, 636*
—— normal women; urinary 17-ketosteroid excretion in, 426*
—— ovariectomy; effect on ketosteroid excretion in normal rat, 795*
—— ovulation as indicated by pregnanediol precipitation test, 234*
—— ovulation, human; prediction of time of, by the rat ovarian hyperemia test, 110
—— transplanted into spleen; effect of castration and pregnancy on, in rats, 667†
PREPARATIONS: *see* Estrogens; Progesterone; Steroids
OVULATION: *see* Menstruation; Ovary, physiology; and Pregnancy

PAIN
—— of osteitis deformans relieved by insulin, 385*
—— relief of, by androgen therapy, in patients with bone metastases from breast cancer, 1314*
PANCREAS: *see also* Blood, sugar; Carbohydrate metabolism; Diabetes mellitus; Insulin
—— hyperglycemic factor extracted from, 669†
—— in diabetes mellitus following Addison's disease (autopsy), 36*
—— in preparation of human insulin for experimental use, 481*
—— insulin content reduced in nondiabetics dying of debilitating disease, 481*
—— islet cell atrophy of, in Addison's disease with diabetes, 403*
—— regeneration of beta cells in, after implantation of PZ insulin, in rabbit, 818*
PANHYPOPITUITARISM: *see* Pituitary disorders
PARA-AMINOHIPPURATE, renal excretion of, in Cushing's syndrome, 13*
PARAPLEGIC MALES; gynecomastia in, 457*
PARATHYROIDS: *see also* Calcium metabolism; Thyroid
—— hyperparathyroidism, with congenital malformation of kidneys, and renal dwarfism, 401
—— pseudohypoparathyroidism, 665†
—— pseudohypoparathyroidism; electrolyte metabolism in; therapy, 862*
—— tetany after surgery of thyroid; increased incidence since use of antithyroid drugs, 999*
—— tetany; incidence of, following total thyroidectomy for toxic goiter, 1048*
PELLET IMPLANTATION: *see* Administration
PENIS: *see also* Androgen and Gonadotropins, effects; Hermaphrodism; Puberty, precocious; Testis
—— effect of androgen and growth hormone on, in castrated, hypophysectomized rats, 679†
PENTOTHAL anesthesia; basal metabolism testing under, 1190*
PHEOCHROMOCYTOMA: *see* Adrenals, tumors
PERSUFFLATION curve, utero-tubal, in myxedema, 285*
PHOSPHATASE: *see* Enzymes
PHOSPHORUS: *see also* Calcium metabolism; Parathyroids
—— balance in Cushing's syndrome with "steroid diabetes," 672†
—— behavior of, in diabetic keto-acidosis, 673†
—— in blood, in acromegaly, 126*
—— in blood, in hypercalcemic syndrome, 1*
—— in serum; relation to hypopotassemia in diabetic ketosis treated with insulin, 1245*
—— metabolism, in pseudohypoparathyroidism, 862*, 665†
PIGMENTATION: *see* Addison's disease; Skin
PIPERIDO-METHYL-BENZODIOXANE (933-F), antagonist of epinephrine, 651†
PITRESSIN: *see* Pituitary, preparations
PITUITARY: *see also* Cushing's syndrome; Gonadotropins
DISORDERS
—— acromegaly, active and inactive; plasma urate in, 749*

PITUITARY (cont.)
DISORDERS (cont.)
—— acromegaly and granulosa cell tumor of ovary, 630*
—— acromegaly, chromophobe adenoma and panhypopituitarism; radioiodine uptake of thyroid in, 342*
—— acromegaly, treatment of, 126*
—— acromegaly; TSH and thyroxine in serum, 653†
—— chromophobe adenoma observed for nine years; effect of androgen therapy, 372*
—— Cushing's syndrome, *see* Cushing's syndrome
—— diabetes insipidus; hypersensitivity to pitressin in treatment of, 650*
—— dwarfism; cellular structure of testes in, 1333*
—— dwarfism, treated with anterior pituitary extract, 655†
—— hypopituitarism as cause of gynecomastia in paraplegic males, 457*
—— hypopituitarism; thyroid collection of I^{131}, and serum PBI in, 430*
—— implications, in hypertrophic pulmonary osteoarthropathy, 297
—— panhypopituitarism; effect of adrenal compounds on thyroid uptake of radioiodine in, 659†
—— panhypopituitarism; spermatogenesis following treatment, 1245*
—— tumor; response of patient to single injection of ACTH in, 661†
—— tumor; urinary prolactin in, 653†
—— tumors of, or near; low serum precipitable iodine in; differential diagnosis *vs.* hypothyroidism, 1292*
GONADOTROPINS: *see* Gonadotropins
HORMONES: *see* Gonadotropins; and Pituitary, preparations
PHYSIOLOGY AND PATHOLOGY
—— anemia of hypophysectomized rats; effects of nonendocrine hemopoietic agents on, 676†
—— sex difference in secretory control and function of, 654†
—— testis-pituitary interrelationship, 113*
PREPARATIONS AND COMPOUNDS
—— exophthalmic and fat-mobilizing principles of pituitary extract; relation to thyrotropic hormone, 913*
—— extract; effect of various dosages and iodination of, on production of exophthalmos, and mobilization of fat in intact and thyroidectomized guinea pigs, 913*, 927*
—— FSH, *see* Gonadotropins

PITUITARY (cont.)
PREPARATIONS AND COMPOUNDS (cont.)
—— gonadotropic hormone, *see* Gonadotropins
—— growth hormone; effect on penis of castrated, hypophysectomized rat, 679†
—— growth hormone, in the treatment of pituitary dwarfism, 655†
—— luteinizing hormone in pseudocyesis, 668†
—— pitressin; hypersensitivity to; relief from benadryl, 650*
—— posterior pituitary extract; shock from, 106
—— prolactin, in urine; assay of, in various endocrine disorders, 653†
Adrenocorticotropic hormone (ACTH): see also Adrenals, physiology
—— adequacy of ACTH function in nutritional deficiencies in the rat, 656†
—— content of ACTH in pituitary gland of rats, 656†
—— effect of large amounts on free and esterified serum cholesterol in normal men, 656†
—— effect of single injection of, in normal subjects and in those with Addison's disease and with pituitary tumor, 661†
—— effect on adrenal cortical hormone in blood of dogs, 658†
—— effect on eosinophiles and uric acid excretion, 109
—— effect on eosinophiles, following major surgery, 662†
—— effect on eosinophiles, in mental disease, 440*
—— effect on exophthalmos and fat mobilization in guinea pigs, 937*
—— effect on urate metabolism, 749*
—— evaluation of adrenal cortex response by, in heat and cold stress, 529*
—— inability of, to deplete ascorbic acid of chick adrenal, 655†
—— metabolic actions and fate of, when administered intravenously in man, in large single dose, 593*
—— production of, inhibited by testosterone therapy, in Cushing's syndrome, 663†
—— regulation of, by adrenal cortical hormones, 656†
Thyrotropic hormone (TSH): see also Thyroid, physiology
—— content of pituitary, in rats treated with tetrabrom- and tetrachlorthyronine, 1107*

PITUITARY (cont.)
PREPARATIONS AND COMPOUNDS (cont.)
Thyrotropic hormone (cont.)
—— in normal and pathologic serum; assayed by stasis tadpole, 653†
—— effect in pituitary dwarfism, 655†
—— effect on metabolism of radioiodine by the thyroid, 171*
—— high production of, as possible cause of myxedema circumscription thyrotoxicum, 883*
—— in patients with tumors at or near the pituitary, 1292*
—— inactivation of, by iodinated pituitary extract; partial restoration by thiouracil, 927*
—— relation to exophthalmic and fat-mobilizing principles of pituitary extract, 913*
—— role in thyroid research, 300
—— thyroid-pituitary apparatus as a servo (feed-back) mechanism, 1429*
—— use of, to induce radioiodine uptake by metastases from thyroid cancer, 1122*, 1138*
PLACENTA: *see* Pregnancy; Uterus
—— chorionic gonadotropin from, *see* Gonadotropins
PLASMA: *see* Blood
PLUMMER, HENRY S., subject of 1949 presidential address of American Goiter Association, 967*
PNEUMOTHORAX following thyroidectomy, 987*
POLYETHYLENE GLYCOL wax, nontoxic vehicle for intraoral tablets of DOCA, 1324*
PORPHYRIA simulating anorexia nervosa, 683†
POSTERIOR PITUITARY: *see* Pituitary, disorders and preparations
POSTGRADUATE ASSEMBLIES IN ENDOCRINOLOGY: *see* Association, post graduate assemblies; American Diabetes Association; Laurentian Hormone Conference; and University of California
POTASSIUM: *see also* Electrolytes
—— deficiency; a mechanism of, in alkalosis, 676†
—— deficiency, associated with diabetic acidosis, 397
—— hypokalemia; electrolyte and protein metabolism in, 691*
—— hypokalemic alkalosis in Cushing's syndrome; effect of potassium chloride and testosterone therapy on, 663†
—— hypotassemia in diabetic keto-acidosis, 673†
—— hypopotassemia; symptoms of, 1259*
POTASSIUM (cont.)
—— in serum; effects of therapy on in Addison's disease with diabetes, 403*
—— metabolism following ACTH intravenously, in man, 593*
—— metabolism, following single dose of DOCA, 660†
—— metabolism; the thyroid as a regulator of, 106
—— use of, in therapy, 691*
PRECOCIOUS PUBERTY: *see* Puberty, precocious
PREGNANCY: *see also* Breast; Estrogens; Fetus; Gonadotropins; Menstruation; Ovary; Pregnanediol; Progesterone; Sterility; Uterus
—— and labor; changes in leucocytes and circulating eosinophiles during, 714*
—— effect of, on ovary transplanted into spleen, in unilaterally castrate rats, 667†
—— increase of urinary gonadotropin in, by parenteral administration of chorionic gonadotropin, 268*
—— pseudocyesis; hormonal pattern in, 668†
—— renal clearance of chorionic gonadotropin in, 615*
—— serum precipitable iodine concentrations during, 299
—— serum protein-bound iodine increased in; possible cause, 768*
—— urinary prolactin, pre- and postpartum, 653†
—— urine; conjugated sulphates of estrogens in, 667†
COMPLICATIONS AND SEQUELAE
—— abortion; preventive treatment with chorionic gonadotropin, 268*
—— abortion, threatened; evaluation of the Guterman pregnanediol, test in, 110, 111
—— abortion, threatened; management with large doses of stilbestrol, 669†
—— as a factor in etiology of diabetes, 48*
—— complicated with thyrotoxicosis; treatment with thiouracil, 903*
—— eclampsia and pre-eclampsia; urinary corticosteroids in, 1436*
—— eclampsia; changes in eosinophiles in, 714*
—— edema of, and pre-eclampsia; cortical steroid excretion in, 319*
—— fetal death; test for, 402
—— in Addison's disease; hormone and electrolyte metabolism, 514*
—— in the diabetic, 395
DIAGNOSIS (Tests)
—— Galli Mainini's test; care of toads

PREGNANCY (cont.)
DIAGNOSIS (Tests) (cont.)
and frogs for, 1372*; results with, 1372*, 400
—— pregnanediol, *see also* Pregnanediol
—— pregnanediol excretion as a test for, 852*, 110, 111, 399, 479
—— pregnanediol excretion in cases of blighted ovum, 676†
—— pregnanediol precipitation test; further observations; comparison with Friedman test, 234*
—— sperm release in frogs; hormonal factors involved, and comparison with ovarian hyperemia test, 668†
—— test, using the male batrachia, 1372*, 668†, 399, 400
—— two-hour test, based on rat ovary hyperemia, 479
PREGNANEDIOL: *see also* Estrogens; Progesterone; Pregnancy
IN URINE
—— as a test of pregnancy, 852*
—— effect of alpha-tocopherol on, in normal and in sterile women, 743*
—— Guterman test for; evaluation of, 110, 111
—— in cases of blighted ovum, 676†
—— new colorimetric method for the determination of, 399
—— precipitation test; further observations, 234*
—— simplified technique for quantitative colorimetric estimation of, 479
—— sodium, glucuronidate, in pregnant woman with Addison's disease, 514*
PREGNENOLONE: *see* Progesterone
PRESIDENTIAL addresses; *see* American Goiter Association
PROGESTERONE: *see also* Estrogens; Menstruation; Pregnancy; Steroids
—— and anhydrohydroxyprogesterone; comparison of oral, sublingual and intramuscular routes of administration, 736*
—— effect on metabolism of estrogen, 557*
—— pregnanediol, *see* Pregnanediol
—— pregnenolone, in treatment of male infertility, 480
—— therapy (i.m. and pellets) of human uterine leiomyomas, 1273*
—— withdrawal test, in amenorrhea, 110
PROGRAMS: *see* Association; American Diabetes Association; American Goiter Association; Laurentian Hormone Conference
PROLACTIN: *see* Breast; Pituitary preparations and compounds; Gonadotropins
PROPIONIC ACID: *see also* Androgens and Estrogens (propionates)
—— phenyl diiodohydroxy phenyl; in study of organic *vs.* inorganic iodine, 1080*
PROPYLTHIOURACIL: *see* Thiouracil
PROSTATE AND SEMINAL VESICLES: *see also* Androgens; Gonadotropins; Testes
—— carcinoma and adenoma of; urinary 17-ketosteroids in, 400
—— response of seminal vesicles and coagulating glands to testosterone, in mice; effect of crude folic acid antagonists on, 674†
PROTAMINE-ZINC INSULIN: *see* Insulin
PROTEIN: *see also* Blood; Creatinine; Muscle; Nitrogen; Uric Acid; Urine, and under various endocrine glands
—— albumin of serum; relation to precipitable iodine in, 107
—— catabolism in diabetes mellitus with thyrotoxicosis; effect of testosterone on, 671†
—— low-protein diet malnutrition in the rat; adequacy of ACTH function in, 656†
—— metabolic abnormality of, in Cushing's syndrome; study by S^{35}-labeled-methionine, 662†
—— of diet; effect on ability of liver to inactivate estradiol in the rat, 675†
—— of serum, in tumors at or near the pituitary, 1292*
——protein-bound iodine of serum; *see* Blood, iodine
—— proteolytic activity, in the study of the thyroid gland, 298
PSEUDOCYESIS, hormonal pattern in, 668†
PSEUDOHERMAPHRODISM: *see* Hermaphrodism; Adrenals; Ovary; Testis
PSEUDOHYPOPARATHYROIDISM, 862*, 665†
PSYCHONEUROSIS: *see also* Brain; Emotion; Mental; Nervous system
—— versus hyperthyroidism: differential diagnosis of; by basal metabolism testing under pentothal anesthesia, 1190*; by antithyroid drugs, 1054*
PTEROYLGLUTAMIC ACID: *see* Vitamins, folic acid
PUBERTY: *see also* Adrenals; Growth; Ovary; Testis; Virilism
—— physical growth during adolescence, 400
PRECOCIOUS
—— role of adrenal cortex in, 674†
—— unusual case of, associated with ovarian dysgerminoma (hormone

PUBERTY (cont.)
PRECOCIOUS (cont.)
assays), 1349*
—— urinary prolactin in, 653†
PULMONARY CLEARANCE of radioactive iodine, 1080*
PYRIBENZAMINE: *see* Antihistaminic drugs

RADIOACTIVE
—— bromine compounds (dibromestrone) 112
—— carbon, in study of diabetes, 1238*
—— estrogens (dibromestrone), 112
—— iodine, *see* Iodine, radioactive
—— sulphur, *see* Sulphur
—— thyroglobulin and thyroxine, *see* Thyroid, preparations
RADIOAUTOGRAPHY: see Iodine, radioactive
RADIOIODINE: *see* Iodine, radioactive
REACTIONS:
—— chemical; *see* Methods; Tests
—— to drugs, *see* Allergy; Iodine, radioactive; Thiouracil; and under various glandular preparations
RECIPIENTS, of Awards and Fellowships, *see* Association, Awards; and American Goiter Association
RENAL: see Kidney
REPRODUCTION: *see* Menstruation; Ovary; Pregnancy; Sterility; Testis
RESEARCH FELLOWSHIPS: *see* Awards
REVIEWS, endocrine, 171*, 557*
RHEUMATISM: *see* Arthritis
ROENTGEN RAYS
—— contrast radiography of uterus, before and after progesterone therapy for uterine leiomyoma, 1273*
—— effect of, on urinary 17-ketosteroids, in ankylosing spondylarthritis, 79*
—— in therapy of lymphosarcoma of thyroid, 1043*
—— in therapy of thyroid cancer, 1023*
—— in thyroid therapy; appearance of Hürthle cells following, 874*
—— in treatment of acromegaly, 126*
—— in treatment of hyperthyroidism; effect on radioiodine uptake, 342*
—— therapy; question of necessity in nonencapsulated sclerosing thyroid tumors, 1216*
ROSTER OF THE ASSOCIATION, request: *see* Association, roster
RUTABAGA ROOT; goitrogen (thiooxazolidone) in, 1069*

SALINE: *see* Sodium, chloride
SALT: *see* Sodium, chloride
SCHERING FELLOWSHIP: *see* Association, Awards
SCOTTISH diabetic clinic; survey of, 48*
SEMEN: *see* Prostate; Testis, spermatozoa
SEMINAL VESICLES: see Prostate; Testis
SEPSIS: *see* Infection
SERTOLI CELL TUMORS: see Ovary, tumors; Testis
SERUM: *see* Blood
SEX: *see also:* Breast; Climacteric, Hermaphrodism; Menstruation; Ovary; Pregnancy; Prostate; Testis; Uterus
—— difference in rate of radioiodide uptake, 430*
—— difference in secretory control and function of pituitary, 654†
—— difference in urate metabolism, 749*, 666†
—— effect on urinary excretion of 17-ketosteroids, 426*
—— hormones, *see* Androgens; Estrogens; Gonadotropins; Progesterone; Steroids
—— in relation to type of tissue replacement in hyperplastic thyroid gland, 1202*
—— incidence in diabetes mellitus, 48*
—— sexual precocity, *see* Adrenals, disorders; Puberty, precocious
SHOCK: *see also* Insulin; Stress
—— electrically induced; changes in eosinophiles after, 440*
—— electrically induced; changes in urinary uric acid-creatinine ratio after, 548*
—— from posterior pituitary extract, 106
—— insulin; in therapy, *see* Insulin
SKIN: *see also* under various endocrine disorders
—— localized, solid edema, in association with exophthalmic goiter; biopsy, 883*
—— nevi, abundant; associated with rudimentary testes, dwarfism and congenital malformations, 1333*
—— nodules in pseudohypoparathyroidism, 862*
—— pigmentation, *see* Addison's disease
—— tophi of gout, 749*
SMEARS: *see also* Climacteric: Menstruation
—— urethral, in the female; relation to smears of urinary sediment; effect of estrogens on, 1362*
—— vaginal, *see* Vagina
SODIUM: *see also* Chloride; Electrolytes; and various endocrine glands
—— and chloride excretion; relative independence of, 368*
—— chloride, hypertonic; renal excretion of, in Cushing's syndrome, 13*

SODIUM (cont.)
—— citrate, in treatment of hypercalcemic syndrome, 1*
—— deprivation; changes in urinary steroids following, 661†
—— determination of, in biologic fluids; rapid colorimetric method for, 95*
—— in serum, increased in diabetic ketoacidosis, 1245*
—— metabolism following ACTH intravenously, in man, 593*
—— retention following single dose of DOCA, 660†
—— saline administration; renal function in normal and adrenalectomized rats following, 658†
—— salts; effect of treatment with, in hypokalemia, 691*
—— salts in the potentiation of the hypertensive effects of DOCA, 109
SPERMATOZOA: *see* Testis, spermatozoa
SPLEEN
—— enlarged in corticoadrenal tumor, with goiter and gynecomastia, 255*
—— ovary transplanted into; effect of castration and pregnancy on, in rats, 667†
SPONDYLARTHRITIS: *see* Arthritis
SQUIBB AWARD: *see* Association, awards
STERILITY: *see also* Menstruation; Pregnancy; Ovary; Testis
—— basal temperature in sterile women, 110
—— blighted ovum; pregnanediol excretion in patients with, 676†
—— causes of, in West African Negroes, 111
—— development of spermatogenesis in hypogonadism, 1245*
—— effect of alpha-tocopherol on pregnanediol excretion in, 743*
—— effects of small doses of testosterone propionate on spermatogenesis, 666†
—— fertility of male gout patients, 497*
—— impotence in paraplegic males with gynecomastia, 457*
—— in the female; facts and fantasy in the study of, 112
—— in the male; treatment with pregnenolone, 480
—— infertile men; antihormones complicating treatment of, 213*
—— infertile men; effect of pituitary antihormone on sperm, testis and urinary gonadotropins in, 355*
—— spermatogenesis following treatment for eunuchoidism, 163*
STEROIDS
—— adrenal, *see also* Adrenals, preparations and compounds
STEROIDS (cont.)
—— androgens, *see also* Androgens
—— corticoids, urinary, 659†
—— corticosteroids, corticoids, cortin, *see also* Adrenals, preparations and compounds
—— determination of, *see also* Methods
—— estrogens, *see* Estrogens
—— hormones, allergy to, 681†
—— neutral lipid-reducing; effect of ACTH intravenously on, in man, 593*
—— neutral lipid-soluble reducing substances; excretion of, by infants, 646*
—— 11-oxysteroids; effect of Compound E on, in Addison's disease, 660†
—— 11-oxysteroids; effect of testosterone with ACTH on, in Cushing's syndrome 663†
—— progesterone, *see* Progesterone
—— reducing, in urine, in Cushing's syndrome, 663†
—— "steroid diabetes," in Cushing's syndrome; 11-oxysteroids and Compound F in, 672†
—— urinary; relation to growth of axillary hair, 665†
17-KETOSTEROIDS (URINARY)
—— during estrus cycle in normal female rats; effect of ovariectomy, and of adrenalectomy, 795*
—— effect of a single injection of ACTH on, in normal subjects and in those with Addison's disease and with pituitary tumor, 661†
—— effect of Compound E on, in Addison's disease, 660†
—— effect of heat, cold and exercise stress on, in men, 529†
—— effect of roentgenotherapy on, in ankylosing spondylarthritis, 79*
—— effect of testosterone with ACTH on, in Cushing's syndrome, 663†
—— following ACTH intravenously in man, 593*
—— following salt deprivation and administration of DOCA, 661†
—— in Addison's disease, 1324*
—— in Cushing's syndrome; comparison of, in adrenal tumor *vs.* hyperplasia, 680†
—— in gout, 497*, 666†
—— in idiopathic hirsutism, 795*
—— in idiopathic hyperuricemia, and in rheumatoid arthritis or spondylitis, 497*
—— in male dog with feminizing testicular tumor, 579*
—— in male hypogonadism; effect of testosterone on, 1245*

STEROIDS (cont.)
17-KETOSTEROIDS (URINARY) (cont.)
—— in masculinizing tumor of ovary, 774*
—— in men with tumors at or near the pituitary, 1292*
—— in normal men, and in eunuchoid men during sex hormone therapy, 113*
—— in porphyria, 683†
—— in precocious puberty associated with ovarian dysgerminoma, 1349*
—— in pregnant women with Addison's disease, 514*
—— in prostatic carcinoma and adenoma, 400
—— in relation to metabolism of circulating testosterone, 665†
—— in testicular chorioma, 615*
—— in Turner's syndrome in a male, 1333*
—— in uterine leiomyoma; effect of progesterone therapy, 1273*
—— in virilizing Leydig cell tumor of ovary, 486*
—— normal values in relation to age and sex, 426*
STILBESTROL: *see* Estrogens
STRESS: *see also* Mental disease
—— effect on adrenals and on ACTH of pituitary in rats, 656†
—— effect on liver fat, in mice, 657†
—— emotional; role of, in survival of treated adrenalectomized rats, 678†
—— heat, cold, and exercise; hormonal alterations in men exposed to; effect of ACTH on, 529*
—— major surgery; effect on adrenal cortical activity, 662†
—— response of white blood cells to, 678*, 714*
SUBJECT INDEX to Volume 9 (1949), 1455
SUGAR: *see* Blood, sugar; Carbohydrate metabolism; Diabetes mellitus; Insulin; Adrenals, preparations and compounds
SULPHUR: *see also* Protein; Thiouracil
—— conjugated sulphates of estrogens, in human pregnancy urine; use of phenolsulphatase in analysis, 667†
—— radioactive; in study of metabolism and tissue distribution of, in rat, 664†
—— S^{35}-labeled-methionine; in study of protein metabolic abnormality of Cushing's syndrome, 662†
SUPRARENALS: *see* Adrenals
SYMPATHICOTROPIC (LEYDIG) CELL tumor of ovary, with virilism, 486*
SYNDROME
—— adrenogenital, *see* Adrenals
—— Cushing's; *see* Cushing's syndrome
—— Fröhlich's, *see* associated with Ovary, Testis, and Pituitary, disorders
—— hypercalcemic, associated with androgenic and estrogenic therapy, 1*
—— hypoglycemic, with corticoadrenal tumor, 255*
—— menopausal, *see* Climacteric
—— Turner's in a male, 1333*

TADPOLE, stasis, in the assay of thyroxine and TSH in normal and pathologic serum, 653†
TEMPERATURE
—— heat; hormonal alterations in men, exposed to; effect of ACTH, 529*
BASAL BODY
—— correlation with excretion of pregnanediol, 234*
—— correlation with pregnanediol excretion; effect of alpha-tocopherol, 743*
—— during ovarian cycle, 714*
—— in sterile women, 110
—— relation to serum protein-bound iodine, during normal menstrual cycle, 768*
TESTIS: *see also* Androgens; Gonadotropins; Hermaphrodism; Prostate; Sterility
—— estrogen production by, 579*
—— evidence for second hormone of, 113*, 579*
—— interrelationship with pituitary, 113*
—— Leydig cell tumor of ovary, with virilism, 486*
—— normal males; differentiation of urinary gonadotropins in, 636*
—— normal men; 17-ketosteroid excretion in, 426*
—— tissue slices; ability to synthesize testosterone from androstenedione-3, 17, in vitro, 674†
DISORDERS
—— chorioma of; renal clearance of chorionic gonadotropin in, 615*
—— estrogen-producing Sertoli cell tumors of, (androblastoma tubulare lipoides), 301*
—— feminizing Sertoli cell tumor of, in male dog, 579*
—— precocious puberty, *see* Puberty, precocious
—— pseudohermaphrodism; *see* Hermaphrodism
Hypogonadism (includes eunuchism, eunuchoidism, Fröhlich's syndrome, etc.), *see also* Pituitary, disorders
—— castrated rats; androgenic acti-

TESTIS (cont.)
DISORDERS (cont.)
Hypogonadism (cont.)
vity of new esters of testosterone in, 679†
—— cellular structure of testis in Turner's syndrome and in hypophyseal dwarfism, 1333*
—— eunuchoidism; development of spermatogenesis in, 1245*
—— eunuchoidism; inability of testosterone to reduce urinary gonadotropin in, 113*
—— eunuchoidism with pituitary tumor; effect of androgen therapy, 372*
—— infertile men; antihormone formation complicating treatment of, 213*
—— infertile men; effect of pituitary antihormone on sperm, testis and urinary gonadotropins in, 355*
—— paraplegic males with gynecomastia; testis in, 457*
—— rudimentary testes, delayed growth, and congenital malformations (Turner's syndrome in a male), 1333*
—— spermatogenesis in, following treatment; coincidental neoplasm, 163*
—— *therapy, see* Androgens; Gonadotropins
PREPARATIONS AND COMPOUNDS: *see* Androgens; Steroids
SPERMATOZOA; *see also* Sterility
—— almost completely suppressed in case of adrenal cortical carcinoma, 451*
—— arrested development, in case of Addison's disease and diabetes mellitus, 403*
—— detachment from toad or frog, in test for pregnancy, 1372*, 399, 400
—— development of spermatogenesis in hypogonadism, 1245*
—— effect of pituitary antihormone on sperm, in infertile men, 355*
—— effect of pregnenolone therapy on, in infertility, 480
—— effect of small doses of testosterone propionate on, 666†
—— in paraplegic males with gynecomastia, 457*
—— sperm release in frog; hormonal factors involved in, 668†
—— sperm release in toad; used to differentiate gonadotropins, 297
—— spermatogenesis following treatment for eunuchoidism, 163*
TESTOSTERONE and compounds: *see* Androgens; Steroids
TESTS: *see also* Blood; Methods; Pregnancy, tests; and under specific substances and diseases
—— Aschheim-Zondek, in precocious puberty associated with ovarian dysgerminoma, 1349*
—— for pregnancy, *see* Pregnancy, diagnosis (tests)
—— for threatened abortion, *see* Pregnancy, tests
—— Friedman; in adrenal cortical carcarcinoma in a male, 451*
—— Friedman; in masculinizing tumor of ovary, 774*
—— Guterman test, *see* Pregnanediol
—— insulin tolerance, *see* Insulin
—— ovarian hyperemia test for gonadotropins, 636*, 654†, 479
—— pregnanediol precipitation, *see* Pregnanediol; Pregnancy, tests
—— sugar tolerance, *see* Blood, sugar
—— uterine weight test for gonadotropins, 636*, 654†
TETANY: *see* Calcium; Parathyroids; Thyroid
TETRABROMTHYRONINE, effect in myxedema and in hyperthyroidism, 1099*
TETRACHLORTHYRONINE, effect in myxedema, 1099*
THIOCYANATE goiter, with myxedema, 446*
THIOCYTOSINE, as a goitrogen, 801*
THIOOXAZOLIDONE; a naturally occurring goitrogen; relation to pathogenesis of simple goiter, 1069*
THIOURACIL: *see also* Antithyroid drugs; Iodine; Thyroid
—— action of antithyroid drugs, studied by radioiodine, 171*
—— effect on uptake of radioactive iodine in the rat, 1080*
—— Hürthle cells in thyroid, consequent to treatment with, 874*
—— in the restoration of thyrotropic activity of iodinated pituitary extract, in guinea pigs, 927*
—— preoperatively; favorable and unfavorable effects, 999*
—— therapy in pheochromocytoma with excessive hypermetabolism, 782*
—— treated mice; response to stress, 657†
—— treated rats; effects of thyroxine, and tetrabrom- and tetrachlorthyronine in, 1107*
—— treated rats; thyroxine analogues tested in, 937*

THIOURACIL (cont.)
COMPOUNDS
—— and propylthiouracil; effect of prolonged treatment with, on collection of radioiodine by metastatic cancer of the thyroid, 1138*
—— and propylthiouracil, in treatment of hyperthyroidism, 1232*
—— and propylthiouracil in treatment of postoperative hyperthyroidism, 1054*
—— and propylthiouracil, in treatment of thyrotoxicosis complicating pregnancy, 903*
—— correlation of chemical structure and antithyroid effect of, 107
—— in treatment of thyrotoxicosis, 300
—— iodinated thiouracils; thiocytosine, and 2 (acetic acid) propylthiouracil; antithyroid action of, 801*
—— propylthiouracil; effect on blood cholesterol and arterial intima in the rat, 106
—— propylthiouracil in the treatment of hyperthyroidism, 330*, 107, 297
—— propylthiouracil therapy; effect on radioiodine uptake, 342*
—— propylthiouracil; toxic reactions to, 330*
—— propylthiouracil; treatment of angina pectoris with, 106
—— thiocyanate goiter, *see* Thiocyanate
—— thiourea; metabolism and tissue distribution of, in rat, measured with radioactive sulphur, 664†
THIOUREA: *see* Thiouracil; Thyroid
THYMUS: *see* Lymphocytes; Lymphoid tissue
THYROID: *see also* Antithyroid drugs; Eyes; Iodine; Thiouracil
DISORDERS
—— a review, 974*
—— diagnosis; substitution of thyroid radioiodine uptake for BMR, in routine clinical practice, 664†
—— endemic goiter in Yunnan province, 684†
—— goiter; effects of thyroxine, tetrabrom- and tetrachlorthyronine on development of, in rats receiving thiouracil, 1107*
—— goiter, with corticoadrenal tumor, gynecomastia and hepatosplenomegaly, 255*
—— Hashimoto's disease and exhaustion atrophy; significance of cellular involution of thyroid in, 874*
—— Hashimoto's disease; chronic thyroiditis, 980*
THYROID (cont.)
DISORDERS (cont.)
—— Hashimoto's thyroiditis; Delphian lymph node in, 1012*
—— lateral aberrant thyroid tumors in differential diagnosis of malignancy, 1031*
—— lymphosarcoma, 1043*
—— nodules; preoperative estimation of function of, by radioautography (method), 1171*
—— nonencapsulated sclerosing tumors; nature of, 1216*
—— nontoxic nodular goiter; incidence of cancer in, 1007*, 1012*
—— simple goiter; dietary factors (thiooxazolidone) in pathogenesis of, 1069*
—— sporadic goiters; treatment with bismuth salts, 462*
—— study and treatment with radioiodine 171*, 342*
—— thyroidectomy in the treatment of toxic and nontoxic goiter; operative mortality, 1232*
—— thyroidectomy; mediastinal emphysema and pneumothorax following, 987*
—— thyroidectomy used to induce uptake of radioiodine by metastases from thyroid cancer, 1122*, 1138*
—— thyroiditis; statistical study, 1202*
Cancer—Carcinoma
—— adenocarcinoma, metastatic; distribution of radioiodine in a patient with, (necropsy), 1379*
—— degrees of malignancy, 1031*
—— destruction of metastases from, by treatment with radioiodine, 1122*, 1138*
—— diagnosis; Delphian lymph nodes an early sign, 1012*
—— function of various types of, studied by radioautography, 1153*, 1171*
—— Hürthle cell carcinomas, 1023*, 1153*
—— incidence of, in nodular goiter, 1007*, 1012*, 1171*
—— natural history of; review of 301 cases, 1023*
—— radioiodine in serum, urine and expired air in, 1080*
—— study of functional capacity, by means of radioiodine, 1012*, 1122*
—— study of, with radioiodine, 171*, 342*, *see also* Iodine, radioactive
—— surgical treatment of, 1422*

THYROID (cont.)
DISORDERS (cont.)
Cancer—Carcinoma (cont.)
—— treatment, *see also* Iodine, radioactive
Hyperthyroidism (exophthalmic goiter, Graves' disease, thyrotoxicosis, toxic adenoma)
—— and acromegaly, 126*
—— and diabetes mellitus; effect of testosterone on products of fat and protein catabolism in, 671†
—— and malignant exophthalmos; studied by radioiodine, 342*
—— cellular involution of thyroid in, 874*
—— clinical significance of lymphocytic and fibrocytic replacements in hyperplastic thyroid; effect of age and sex, 1202*
—— complicating pregnancy; treatment with goitrogens, 903*
—— crisis of, following surgical removal of metastasis of thyroid cancer to bone, 1122*
—— differential diagnosis with basal metabolism testing under pentothal anesthesia, 1190*
—— effect of cessation of lactation and return of menstruation on, 330*
—— exophthalmos, *see also* Eyes
—— following treatment with large doses of radioiodine for thyroid cancer, 1138*
—— hyperfunction of thyroid nodules studied by radioautography, 1171*
—— in young dissimilar twins, 298
—— mild, in early stages of Hashimoto's disease, 980*
—— myxedema circumscriptum thyrotoxicum, 883*
—— nonencapsulated sclerosing tumor of thyroid associated with, 1216*
—— thirty-five years' experience with, 974*
—— thyroid I^{131} and I^{127} collection in; influence of iodide ion and of antithyroid drugs on, 941*
—— thyroid-stimulating hormone (TSH) and thyroxine in serum, 653†
—— thyroid-stimulating, or thyrotropic hormone (TSH) in, *see also* Pituitary, preparations and compounds
—— thyrotoxicosis factitia, 377*, 1432*
—— thyrotoxicosis; incidence in diabetes mellitus, 48*

THYROID (cont.)
DISORDERS (cont.)
Hyperthyroidism (cont.)
—— thyrotoxicosis; myogram in, 401
—— toxic nodular and diffuse goiter; incidence of cancer in, 1007*, 1012*
—— urinary excretion of radioiodine in, 171*, 299, *see also* Iodine, radioactive
—— width of adrenal cortex in, 158*
Therapy, see also Antithyroid drugs; Iodine; Thiouracil
—— antithyroid drugs in treatment of postoperative hyperthyroidism, 1054*
—— evaluation of current methods of treatment, 1232*, 299, 300
—— mediastinal emphysema and pneumothorax following thyroidectomy for, 987*
—— surgery the most satisfactory method of treatment; favorable and unfavorable effects of preoperative antithyroid drugs, 999*
—— total thyroidectomy, 1048*
—— with bismuth salts, 462*
—— with iodinated thiouracils, and thiocytosine, 801*
—— with iodine, *see* Iodine
—— with propylthiouracil, 330*, 107, 297 (*see also* Thiouracil compounds)
—— with radioactive iodine, 29*, 171*, 298 (*see also* Iodine, radioactive)
—— with roentgen rays, *see* Roentgen rays
—— with tetrabromthyronine, 1099*
—— with thiouracil and compounds, *see* Thiouracil
Hypothyroidism
—— behavior of labeled iodocasein in; treatment with iodocasein, 828*
—— behavior of labeled thyroglobulin and thyroxine in, 1392*
—— differential diagnosis *vs.* tumors at or near the pituitary, 1292*
—— distribution and fate of oral and i.v. radioactive racemic thyroxine in, 1406*
—— effect of antithyroid drugs, *see* Antithyroid drugs; Thiouracil
—— effect of *d*-thyroxine and tetrabrom- and tetrachlorthyronine in, 1099*
—— following radioiodine therapy for metastases of thyroid car-

THYROID (cont.)
DISORDERS (cont.)
Hypothyroidism (cont.)
cinoma 1122*, 1138* (*see also* Iodine, radioactive)
—— following surgical treatment of hyperthyroidism; 999*, 299; effect of antithyroid drugs on incidence, 999* (*see also* Thyroid, disorders, hyperthyroidism)
—— following total and subtotal thyroidectomy for Hashimoto's disease, 980*
—— following total thyroidectomy for toxic goiter, 1048*
—— following treatment of hyperthyroidism with radioiodine, 29*, 171*, 1232* (*see also* Iodine, radioactive)
—— myxedema circumscriptum thyrotoxicum, 883*
—— relation to type of parenchymal replacement in hyperplastic thyroid gland, 1202*
—— significance of Hürthle cells in thyroid in, 874*
—— studied by radioiodine, 342*
—— *therapy*, with thyroid compounds, *see* Thyroid preparations and compounds
—— thirty-five years' experience with, 974*
—— thyroid collection of I^{131}, and serum PBI in, 430*
—— TSH and thyroxine in serum, 653†
—— urinary excretion of radioiodine in, 171* (*see also* Iodine, radioactive)
—— utero-tubal persufflation curve in, 285*
—— with goiter, following thiocyanate therapy, 446*
PHYSIOLOGY AND PATHOLOGY
—— activity during heat and cold stress, in men, 529*
—— as a regulator of potassium metabolism, 106
—— cellular involution in, in various states, 874*
—— clinical significance of lymphocytic and fibrocytic replacements in hyperplastic thyroid gland, 1202*
—— clinical *vs.* pathologic findings in thyroid cancer, 1031*, 1043*, 1047*
—— clinicopathologic studies, *see* Thyroid, disorders
—— effect of radioiodine on structure of thyroid and surrounding tissues, 29*

THYROID (cont.)
PHYSIOLOGY AND PATHOLOGY (cont.)
—— function in man, studied by radioiodine, 342*
—— function; relation to adrenal function, studied by radioiodine, 659†
—— function; studies of, *see also* Iodine, radioactive
—— *hormone*, *see also* Thyroid, preparations
—— hormone; peripheral utilization of; possible influence of sex hormones upon, 430*
—— mechanism of thyroid hormone secretion visualized by radioiodine, 149*
—— metabolism of the thyroid hormone, studied by radioactive thyroid compounds, 1392*, 1406*
—— pathology of thyroid cancer, 1422*
—— possible involvement in mobilization of fat to liver, in the mouse, 657†
—— proteolytic activity in the study of the thyroid gland, 298
—— radioautography in the study of, *see* Iodine, radioactive
—— research; present day trends in, 300
—— significance of colloid relative to concentration of radioiodine in, 1153*
—— thyroidectomized guinea pigs; effect of various doses of pituitary extract on production of exophthalmos, and mobilization of fat in, 913*
—— thyroid-pituitary apparatus as a servo(feed-back) mechanism, 1429*
—— *thyrotropic hormone* (*thyroid-stimulating, TSH*): *see* Pituitary, preparations
—— total iodine accumulation and clearance in, in euthyroidism and hyperthyroidism; effect of iodide on, 941*
—— uptake of radioactive sulphur, by in the rat, 664†
—— weight and iodine content of; effects of thyroxine and tetrabrom- and tetrachlorthyronine on, 1107*
PREPARATIONS AND COMPOUNDS
—— desiccated thyroid; effect on amino acid oxidase activity in the rat, 684†
—— desiccated thyroid; effect on radioiodine uptake of thyroid gland, 342*
—— desiccated thyroid; effect on uterotubal persufflation curve in myxedema, 285*
—— desiccated thyroid ingestion, causing thyrotoxicosis factitia, 377*; 1432*

THYROID (cont.)
PREPARATIONS AND COMPOUNDS (cont.)
—— globulin; absorption and clinical effect of a large single dose, 377*
—— hormone; direct estimation of rate of formation of, in man, 941*
—— hormone; mechanism of secretion visualized by radioiodine, 149*
—— hormone; study of hormonal *vs.* "spurious" protein-bound iodine of serum, 1080*
—— hormone; synthesis, studied by radioiodine, 171*
—— labeled thyroglobulin and thyroxine; behavior of in myxedema, 1392*
—— physiologic activity of thyroxine and analogues, tetrabrom- and tetrachlorthyronine, 1099*, 1107*
—— radioactive racemic thyroxine, given orally and i.v.; distribution and fate in myxedema, 1406*
—— thyroid therapy in some mental disorders, 298
—— thyroxine analogues; thyroxine-like and antithyroxine activity of, 937*
—— thyroxine in normal and pathologic sera, assayed by the stasis tadpole, 653†
—— thyroid preparations, with diet, in the prolonged medical treatment of obesity; toxicity, 275*
THYROIDECTOMY: *see* Thyroid
THYROIDITIS: *see* Thyroid disorders
THYROIDOLOGIST, confessions of, 974*
THYROID-STIMULATING HORMONE (TSH): *see* Pituitary, preparations
THYRONINE, and compounds; thyroxine-like and antithyroxine activity of, 937*
THYROTOXICOSIS: *see* Thyroid, disorders, hyperthyroidism
THYROTROPIC HORMONE (TSH): *see* Pituitary, preparations, thyrotropic hormone
THYROXINE: *see* Thyroid, preparations and compounds
TIME factor in weight reduction, 275*
TISSUES: *see also* under various organs
—— calcification of; extensive, in pseudohypoparathyroidism, 862*
—— distribution of circulating testosterone in, 665†
—— distribution of radioiodine in, after injection into rats, 1080*
——distribution of radioiodine in at necropsy, fifty-six hours after oral ingestion by man with thyroid cancer, 1379*
—— fibrocytic replacements in hyperplastic thyroid; statistical study of clinical significance, 1202*
—— fibrous; leimyomas of uterus; progesterone therapy of, 1273*
TOAD: *see also* Gonadotropins; Pregnancy, tests
—— care and maintenance of, for pregnancy test, 1372*
TOCOPHEROL: *see* Vitamins, E
TOXIC ADENOMA: TOXIC GOITER: *see* Thyroid, disorders, hyperthyroidism
TOXIC EFFECTS: *see also* Iodine, radioactive; Thiouracil; and preparations involved
——allergies, *see* Allergy
—— from therapy with radioiodine, 1138*
—— granulopenia during propylthiouracil therapy, 330*
TRANSPLANTATION of ovary into spleen; effect of castration and pregnancy on, in rats, 667†
TRAUMA: *see also* Stress
—— surgical; effect on circulating eosinophiles, 714*
TSH: *see* Pituitary, preparations, thyrotropic hormone
TUMORS: *see also* Cancer; and under organ or form of treatment involved
—— adrenal, *see* Adrenal, disorders; and Cushing's syndrome
—— androblastoma tubulare lipoides, *see* Ovary; and Testis
—— chromophobe adenoma, *see* Pituitary, disorders
—— craniopharyngioma, *see* Pituitary, disorders
—— dysgerminoma, *see* Ovary, disorders
—— feminizing, *see* Adrenals; Breast, gynecomastia; Hermaphrodism; Ovary; Testis
—— function of, studied by radioiodine, *see* Iodine, radioactive
—— goiter, *see* Thyroid
—— histopathology; study of, *see* Iodine, radioactive; and under various endocrine disorders
—— leiomyoma, *see* Uterus
—— Leydig cell, *see* Ovary; Testis
—— masculinizing, *see* Tumors, virilizing
—— pheochromocytoma, *see* Adrenals, tumors
—— Sertoli cell, *see* Ovary; Testis
—— virilizing, *see* Adrenals, Cushing's syndrome; Hermaphrodism; Ovary; Testis; Puberty, precocious; Virilism
THERAPY
— with hormones *see* Androgens; Estrogens; Progesterone; or other preparation concerned

TUMORS (cont.)
THERAPY (cont.)
—— with radioactive iodine; *see* Iodine, radioactive
—— with roentgen rays, *see* Roentgen rays
TURNER'S SYNDROME in a male, 1333*
TURNIP; goitrogen (thiooxazolidone) in, 1069*
TWINS, young, dissimilar; hyperthyroidism, in, 298

UNIVERSITY OF CALIFORNIA Medical School; postgraduate course in endocrinology; announcement of, 472*
UNIVERSITY OF GEORGIA; course in medical illustration, 295
URATE: *see* Uric acid
UREA: *see* Blood; Nitrogen; Protein; Thiourea
URETHAL smears in the female; relation to smears of urinary sediment; effect of estrogens on, 1362*
URIC ACID: *see also* Creatinine; Nitrogen; Protein
—— creatinine ratio, urinary; after shock therapy, 548*
—— creatinine ratio, urinary; in men exposed to heat and cold, 529*
—— excretion; effect of ACTH on, 109
—— in serum and urine, following ACTH intravenously, 593*
—— of serum; in gout, and in idiopathic hyperuricemia, 497*
—— transport and excretion of, in man; sex difference in urate metabolism, 749*
—— urate metabolism in children and in gout, 666†
—— urate metabolism in gout and hyperuricemia, 749*
URINE: *see* also Kidney
—— chemistry of: *see* Methods; Tests; and Urine, constituents
—— effects of administration of various substances on, in health and disease, *see* specific substance used
—— in disease, *see* specific disease
—— pregnancy tests, *see* Pregnancy, diagnosis (tests)
—— renal function, *see* Kidney
CONSTITUENTS
Cellular
—— sediment; smear of, in female; relation to urethral smears, and effect of estrogen on, 1362*
Chemical
—— adrenal compounds, *see* Adrenals; Addision's disease; Steroids

URINE (cont.)
CONSTITUENTS (cont.)
Chemical (cont.)
—— androgens; *see* Androgens; Steroids
—— antidiuretic nonchloruretic substance extracted from urine of normal and cirrhotic subjects, 652†
—— calcium, *see* Calcium; Electrolytes; Parathyroids
—— chloride, *see* Chloride; Electrolytes; Sodium; Addison's disease
—— chorionic gonadotropin, *see* Gonadotropins, in urine; Pregnancy
—— Compound F, *see* Adrenals, compounds
—— corticosteroids (corticoids, cortin, etc), *see* Addison's disease; Adrenals; Steroids
—— creatinine, *see* Creatinine; Nitrogen; Uric acid
—— electrolytes, *see* Electrolytes
—— estrogens (estradiol, estrone, etc.), *see* Estrogens, in urine; Steroids
—— FSH: *see* Gonadotropins, in urine
—— gonadotropins, *see* Gonadotropins, in urine; Pituitary; Pregnancy
—— insulin, *see* Insulin
—— iodine, radioactive, *see* Iodine, radioactive
—— 17-ketosteroids, *see* Steroids
—— lipids, *see* Lipids
—— *methods* for determination of constituents, *see* Methods; Tests
—— nitrogen, *see* Creatinine; Nitrogen; Protein; Uric acid
—— oxysteroids, *see* Adrenals; Steroids
—— pituitary hormones, other than gonadotropins, *see* Pituitary, preparations
—— potassium, *see* Potassium; Electrolytes
—— pregnanediol, *see* Pregnanediol; Pregnancy; Progesterone
—— protein, *see* Nitrogen; Protein
—— radioactive compounds, *see* Radioactive
—— radioactive iodine, *see* Iodine, radioactive
—— sodium, *see* Sodium; Chloride; Electrolytes; Addison's disease
—— steroids, *see* Steroids
—— sugar, *see* Carbohydrate metabolism; Diabetes mellitus; Insulin; Addison's disease; Adrenals
—— uric acid, *see* Uric acid; Nitrogen

UTERUS: *see also* Breast; Climacteric; Estrogens; Menstruation; Ovary; Pregnancy; Vagina
—— abortion, *see* Pregnancy
—— carcinoma of; testosterone propionate therapy in, 401
—— hydatidiform mole; renal clearance of chorionic gonadotropin in, 615*
—— labor, *see* Pregnancy
—— leiomyomas of; progesterone therapy, studied by roentgenograms and endometrial biopsies, 1273*
—— menstruation; *see* Menstruation; Climacteric
—— placenta; chorionic gonadotropin, *see* Gonadotropins
—— pregnancy, *see* Fetus; Pregnancy; Tests
—— uterine and tubal contractions, in study of female infertility, 112
—— uterine weight test (mouse) for total gonadotropins in urine, 636*, 654†
—— utero-tubal persufflation curve in myxedema, 285*
ENDOMETRIUM: *see also* Menstruation
—— adenomatous hyperplasia of, from granulosa cell tumor of ovary, 630*
—— atrophy of, following prolonged progesterone therapy of leiomyoma, 1273*
—— biopsy; correlation with vaginal smear, 673†
—— biopsy; in study of routes of administration of progesterone, 736*
—— blood flow in; action of intravenously injected sex and other hormones on, 111
—— endometriosis; fibromyomata; urinary prolactin in, 653†
—— in pseudocyesis, 668†

VAGINA: *see also* Climacteric; Estrogens; Menstruation; Ovary; Pregnancy; Progesterone; Uterus
SMEAR
—— correlation with endometrial biopsy, 673†
—— effect of therapy on, *see also* Estrogens; Gonadotropins; Progesterone
—— effects of various estrogens on, in menopausal women, 480†
—— glycogen in; limitations as index of estrogen activity, 1359*
—— human; used in the assay of estrogens, 725*
—— in menopause, *see* Climacteric
—— in ovarian dysfunction, *see* Menstruation; Ovary
—— relation to urethral smear, 1362*

VAGINA (cont.)
SMEAR (cont.)
—— unusual in virilizing Leydig cell tumor of ovary, 486*
VAN METER PRIZE AWARD: *see* American Goiter Association
VASCULAR SYSTEM: *see also* Blood; Heart
—— blood pressure, *see also* specific disease e.g., Addison's disease
—— blood pressure; relation to fluid intake; effect of DOCA on, in rats, 478
—— coarctation of aorta associated with abnormal digits, hypo-ovarianism and dwarfism, 622*
—— degenerative vascular lesions and diabetes mellitus, 394
—— vasomotor instability and hypertension; basal metabolism testing under pentothal anesthesia, in differential diagnosis of, 1190*
HYPERTENSION
—— associated with ovarian hypofunction, and other developmental abnormalities, 622*
—— effect of epinephrine antagonist in, 651†
—— essential; cortical steroid excretion, in, 319*
—— essential; eosinophiles, and plasma corticosteroids, CO_2, and CO_2/Cl ratio in, 677†
—— hypertensive effects of DOCA; potentiation by sodium salts, 109
—— in diabetes mellitus, 48*
—— in pheochromocytoma; effect of 933-F; benzodioxane, 651†, 108
—— in pheochromocytoma; effect of hyperventilation and of removal of tumor, 782*
—— relation to alarm reaction, 479
—— thiocyanate therapy for, followed by goiter and myxedema, 446*
—— urinary steroids in; effects of sodium deprivation and of DOCA, 661†
VIRILISM: *see also* Adrenals, disorders; Cushing's syndrome; Hair; Hermaphrodism; Ovary
—— associated with sympathicotropic (Leydig) cell tumor of ovary, 486*
—— in women, during testosterone therapy of metastases of breast cancer, 1314*
—— virilizing tumors of the ovary, 112
—— with tumor of ovary, in postmenopausal woman, 774*
VITAMINS
—— folic acid (pteroylglutamic acid) antagonists; effect on seminal vesicle

VITAMINS (cont.)
response to testosterone in mice, 674†
—— interrelation with estrogens, 557*
—— pantothenic acid; response of white blood cells to, in the rat, 678†
B
—— deficiency in women; inactivation of estrogen by, 402
—— effect on amino acid oxidase activity in the rat, 684†
C
—— ascorbic acid of chick adrenal; inability of ACTH or epinephrine to deplete, 655†
—— in plasma; effect of chorionic gonadotropin therapy on, 268*
D
—— in treatment of pseudohypoparathyroidism, 862*
E
—— effect of alpha-tocopherol on pregnanediol excretion, in normal and in sterile women, 743*
—— synthetic; effect of, in the menopause, 89*

WATER: *see also* Kidney; Urine; Pituitary disorders, diabetes insipidus
—— and electrolyte balance in diabetic treated with insulin for keto-acidosis, 1245*
—— renal clearance in cirrhosis of liver, with and without ascites, 682†
—— renal excretion of, in Cushing's syndrome, 13*
WEBBED NECK, rudimentary testes and dwarfism, 1333*
WEIGHT: *see* Dwarfism; Growth; Nutrition; Obesity

X-RAYS: *see* Roentgen rays

if she is one of *your* patients...

...She depends on your help for a speedy return to gainful occupation. Women seeking employment who are nervous, apprehensive and generally distressed by symptoms of the climacteric, may find it difficult to meet competition. ***"Premarin"*** *offers a solution. Many thousand physicians prescribe this naturally-occurring, oral estrogen because...*

1. *Prompt symptomatic improvement usually follows therapy.*
2. *Untoward side-effects are seldom noted.*
3. *The sense of well-being so frequently reported tends to quickly restore the patient's confidence and normal efficiency.*
4. *This "Plus" (the sense of well-being enjoyed by the patient) is conducive to a highly satisfactory patient-doctor relationship.*
5. *Four potencies provide flexibility of dosage: 2.5 mg., 1.25 mg., 0.625 mg. and 0.3 mg. tablets; also in liquid form, 0.625 mg. in each 4 cc. (1 teaspoonful).*

Ayerst

While sodium estrone sulfate is the principal estrogen in ***"Premarin,"*** *other equine estrogens... estradiol, equilin, equilenin, hippulin ...are probably also present in varying amounts as water-soluble conjugates.*

"PREMARIN"®

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

ESTROGENIC SUBSTANCES (WATER-SOLUBLE)
also known as CONJUGATED ESTROGENS (equine)

Ayerst, McKenna & Harrison Limited 22 East 40th Street, New York 16, New York

4911

Paradoxically, Testosterone, the male sex hormone, has clinical application in women. Theoretically, the menopausal syndrome, dysmenorrhea, and functional bleeding should be corrected by proper therapy with follicular hormone, progesterone, or pituitary gonadotropin.

Testosterone Armour

often is effective when, in actual practice, some cases of these syndromes do not respond to the above therapy.

Available in these three forms:

Testosterone Propionate Armour . . . (for injection) 25 milligrams per cc. in packages of 6—1 cc. ampules, 50—1 cc. ampules, 1—10 cc. vial.

Methyl Testosterone Armour . . . (oral) 25 milligrams per tablet—in boxes of 30 and 100 tablets.

Testosterone Pellets Armour . . . (for subcutaneous implantation) 75 milligrams per pellet—in boxes of 3.

Have confidence in the preparation you prescribe—specify "ARMOUR"

ARMOUR Laboratories

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS